BRITISH MEDICAL JOURNAL

LONDON SATURDAY MARCH 28 1959

AN ASSESSMENT OF LONG-TERM ANTICOAGULANT ADMINISTRATION AFTER CARDIAC INFARCTION

REPORT OF THE WORKING PARTY* ON ANTICOAGULANT THERAPY IN CORONARY THROMBOSIS TO THE MEDICAL RESEARCH COUNCIL

Although anticoagulant drugs are now commonly used in the immediate treatment of the acute phase of cardiac infarction, the value of their continued administration after this stage has not been rigorously assessed. The design and conduct of the pioneer studies allowed no such definitive assessment, and some doubt prevails about the balance of risks and benefits in the long-term administration of anticoagulant preparations designed to prevent further thrombotic episodes. Apart from haemorrhage, other hazards have been reported with the use of such preparations—for example, skin sensitivity and agranulocytosis (MacMillan and Brown, 1953; Kirkeby, 1954). The repeated hospital visits and blood tests required place a considerable burden on the patient and the pathological services. Furthermore, a review of previous studies has shown that there has been little agreement on the efficacy of anticoagulant therapy in lowering the risk of death or recurrent infarction. Amongst those reporting favourably on this form of treatment, Bjerkelund (1957), for example, found a reduction by a third in the death rate from cardiovascular disease as compared with a sixfold lowering effect reported by Manchester (1957). In a condition like ischaemic heart disease, that so frequently maims and kills, some more precise assessment of the risks and benefits, if any, is needed before a major change is made in the care of patients who have already survived the acute stage of an infarction. Again, neither the role of clotting in the production of cardiac infarction nor the exact mode of action of the anticoagulant drugs is as yet clearly understood.

A controlled study of the value of anticoagulants in the prevention of infarction might clarify some of these issues. The main aim of the clinical trial here reported, however, was to establish whether, in patients who had survived at least one month after their most recent infarction, the continuous administration of an anticoagulant drug (phenindione) in doses sufficient to double the one-stage "prothrombin" time would appreciably reduce the risk of recurrence and death below the levels concurrently observed in a series of patients with illnesses of comparable severity not thus treated. At the same time, the complications which might be attributable to this form of treatment were to be determined in the two series.

Some Earlier Studies

Encouraging as many of the previous reports on this subject have been, they are open to criticism on one or more of the following grounds: the heterogeneity of the clinical material included in the same survey, the failure to ensure that the control series was strictly comparable, inequalities in the clinical supervision and subsidiary treatment during the period of follow-up, and a failure to take into account both the timing and the duration of the period of exposure to the risk of recurrent infarction and death. Since Nichol and Fassett (1947) published the first report on the continuous use of dicoumarol in the prevention of recurrent coronary thrombosis, there have been numerous reports of uncontrolled or partially controlled clinical trials. Keyes, Drake, James, and Smith (1953), for example, included in their series of patients given continuous anticoagulant therapy those with refractory anginal pain and others with signs and symptoms of coronary insufficiency which implied, the authors believed, an "impending coronary occlusion." The control patients were consecutive hospital admissions for coronary disease treated in a preceding six-year period without anticoagulants. The difficulty in ensuring equality in a "historical" control of this type is great, and it is clear that such an unselected series as this would include patients who were less seriously ill than those given continuous anticoagulant therapy in the later period.

Owren (1954) compared his results in a series of patients given anticoagulants with expectations of recurrence and death based on published data for patients not thus treated. Here, again, equality in several material respects between the clinical type of the patients

*The members of the Working Party were: Professor Sir George Pickering (chairman), Professor W. M. Arnott, Dr. R. Biggs, Professor H. W. Fullerton, Dr. A. R. Gilchrist, Professor R. B. Hunter, Dr. D. D. Reid, Dr. P. Wood, Dr. J. H. Wright, and Dr. A. S. Douglas (secretary).

The centres taking part in the trial were: Radcliffe Infirmary, Oxford (Dr. J. R. A. Mitchell); Newcastle General Hospital, Newcastle upon Tyne (Dr. W. G. A. Swan, Dr. C. B. Henderson); the General Infirmary, Leeds (Dr. W. Whitaker, Dr. P Nixon, Dr. A. T. Howarth); National Heart Hospital (Dr. W. Brigden, Dr. R. Hudson, Dr. L. G. Davies); London Hospital (Dr. W. Brigden, Dr. L. Thomas); St. Mary's Hospital, London (Dr. E. S. Snell, Dr. G. Rose, Dr. M. Newman, Dr. J. F. Cummins); Royal Infirmary, Edinburgh (Dr. B. Paton, Dr. G. Kellaway, Dr. D. M. O'Sullivan); Royal Infirmary, Manchester (Dr. A. Morgan Jones, Dr. E. G. Wade, Dr. J. Mackinnon, Dr. D. E. Anderson); Western Infirmary, Glasgow (Dr. R. L. Richards, Dr. J. Buchanan, Dr. E. Gale); Royal Infirmary, Cardiff (Professor H. Scarborough, Dr. G. S. Kilpatrick); Bristol Royal Infirmary, Bristol (Professor C. Bruce Perry, Dr. D. W. Barritt); Queen Elizabeth Hospital, Birmingham (Dr. A. G. W. Whitfield, Dr. J. N. Marshall Chalmers); Royal Infirmary, Glasgow (Dr. R. Fife. Dr. J. Stevenson, Dr. J. Maclaurin, Dr. F. Moran, Dr. I. T. Draper); Maryfield Hospital, Dundee (Dr. W. Walker, Dr. C. R. Rizza, Dr. H Watson); Royal Infirmary, Aberdeen (Dr. G. A. McDonald). At these centres numerous other physicians have referred their cases for inclusion in the trial.

The Working Party is indebted to Evans Medical Supplies, Ltd., Imperial Chemical (Pharmaceuticals) Ltd., and Duncan Flockhart and Co. Ltd., for the provision of bulk supplies of phenindione, which were tableted and distributed by Evans Medical Supplies, Ltd., for the purpose of this trial.

and the form of subsidiary treatment which they received has to be assumed. Suzman, Ruskin, and Goldberg (1955) used contemporary controls; but the patients concerned were not randomly allocated to anticoagulant and other treatment groups. The bias inherent in the selection of patients for anticoagulant therapy cannot be readily assessed. In these studies by the Johannesburg group of workers, as in others, the problem of selective withdrawal from the anticoagulant-treated group also appears. Those who stop treatment are unlikely to be essentially similar to those who persevere, and their mortality experiences may differ appreciably. Yet sometimes, as in a paper by Nichol, Phillips, and Jenkins (1954), this contrast has been made the basis of therapeutic assessment.

Toohey (1958) reported one of the few previous British series. He selected for anticoagulant therapy only patients who had had either one serious infarct or repeated less serious ones. His control series consisted of patients admitted not only to his own hospital but also to others in the district. There was thus a risk both of inequality in the clinical type and severity of cases admitted to different hospitals even at the same time, and of differences between hospitals in ancillary methods of treatment or prescribed restrictions in exercise, diet, or smoking. Even if such factors are not of crucial importance where the advantages of the new treatment are large, they may obscure a small but worth-while benefit.

In the natural history of cardiac infarction the death rate falls rapidly in the first few weeks after the acute attack and more gradually thereafter. Comparisons between groups of patients will thus be justified only when both the timing of the period of observation and its duration are taken into account; for the crude case fatality rate depends on the section of the time curve covered by the period of observation. In the study of Nichol *et al.* (1958), for example, the "controls" were followed up for a longer time. For the same reason, the use of tables of survival giving the time scale in rather broad groups of six months or more, such as those of Block *et al.* (1952), which were used by Waaler (1957), may not give an adequate estimate of the expected mortality without anticoagulant therapy. In any event, the variability in the course of the disease and the psychological effects that arise from regular attendance for laboratory test and clinical assessment make it imperative to conduct a clinical trial using cases of similar severity, randomly assigned to anticoagulant and other treatment groups, and followed up with equal care over the same period of observation from the date of admission to the trial. Only two major studies, those of Manchester (1957) and Bjerkelund (1957), have thus far approached this ideal; and it is with their findings that the results of the present investigation can most profitably be compared.

DESIGN AND CONDUCT OF TRIAL

Selection of Patients

Generally speaking, the suitability of patients for inclusion in this trial depended on the presence of certain well-defined clinical criteria of recent cardiac infarction and the absence of any physical conditions which either presaged early death from other causes or might have been aggravated by the use of anticoagulant drugs. The co-operation of the patients themselves was of course essential, and personal difficulties —for example, in transport from a long distance—often excluded patients from participation in the trial.

A pilot run of the trial scheme over a period of seventeen months showed that the set of rules for inclusion originally laid down were too rigid to allow the collection within a reasonable time of a series large enough for informative analysis. On the other hand, inspection of the preliminary results suggested that some relaxation was possible without seriously affecting the homogeneity of the clinical material. The rules as finally amended are given in brackets in the following tabular statement.

Criteria for Inclusion—Initial and, in Brackets, as Revised After 17 Months

Recent infarction. Q-wave evidence of infarction essential. Treated with anticoagulants in the acute stage (not necessarily treated with anticoagulants).

Age: 40–65 (40–69).

Sex: Both sexes.

Time: On 29th day after day of onset of recent infarction (29th–43rd day).

Previous history.—On the basis of clinical history before the onset of the last infarct, and electrocardiograms where available, patients were classified into three groups:

1. Those with *no* previous infarct.
2. Those with *one* previous infarct.
3. Those with *more than one* previous infarct.

Grounds for Exclusion—Either at Initial Consideration or on Subsequent Development During the Course of the Trial

General.—(*a*) Any non-cardiovascular disability likely to cause death within two years. (*b*) Recurrent haemorrhage or a single haemorrhage within the previous six months from any site—for example, peptic ulcer. (*c*) Active peptic ulceration—clinical diagnosis was acceptable. Any other lesion thought likely to lead to haemorrhage. (*d*) Evidence that the patient was a chronic alcoholic. (*e*) Wassermann reaction positive or other signs of syphilis. (*f*) Any likelihood of the patient requiring intensive salicylate therapy. (*g*) Pregnancy. (*h*) Hepatic disease.

Cardiovascular.—(*a*) Malignant hypertension—patients with hypertensive neuroretinopathy. (*b*) Retinal haemorrhage. (*c*) Uncontrolled cardiac failure. (*d*) Cerebrovascular accident. (*e*) Valvular disease of the heart; in particular, aortic stenosis.

Renal.—(*a*) Raised blood urea—two readings over 60 mg. per 100 ml. at intervals of one week in the absence of cardiac failure.

Hypersensitivity to the Drug.—Previous history or development during trial.

Personal.—Any reasons for believing that the patient was unlikely to be able to attend regularly because of travelling, occupational, or other personal difficulties.

[*Note.*—The following conditions were recorded but did *not* exclude the patients from admission to the trial. (*a*) Any cardiac arrhythmia. (*b*) Cardiac enlargement. (*c*) Hypertensive heart disease provided any failure present was controlled by therapy.]

Therapeutic Regimes

Since the aim of the trial was to assess the value of the anticoagulant drug given in doses large enough to interfere appreciably with blood coagulation, one group of patients were given phenindione in doses which increased the prothrombin time, as measured by Quick's one-stage test, to two to two and a half times the control level (the high-dosage group). On the other hand, some control was essential both of the effect of traces of the substance and of the possible psychological effect of the

regular attendance for laboratory test and clinical assessment. The other group of patients were therefore given apparently identical tablets containing only 1 mg. of phenindione (the low-dosage group). Within each hospital centre both groups of patients received the same additional forms of therapy and the same advice about diet and smoking habits.

Allocation of Patients

Prognosis after infarction is generally believed to depend in part on the number of previous attacks in the same patient. Allocation to treatment regimes was therefore based on a primary division of suitable patients according to the number of previous infarcts; and a random distribution of the patients in each centre within these infarct groups was made to high- or low-dosage levels. For each centre, batches of sealed envelopes were prepared, marked according to the previous infarct history grouping, and enclosing a card bearing the dosage level. The order of the allocation was randomly determined. When the clinician in charge at any centre considered that a patient was suitable for inclusion, and had classified him according to his previous infarction history, he obtained the treatment group allocation by opening the next in the appropriate batch of envelopes.

The results of clinical, electrocardiographic, and *x*-ray examination at the time of inclusion in the trial were entered on special record sheets. The details of the present infarction included the presence or absence of pain, shock, and evidence of cardiac failure, while specific inquiries were made about Q-wave changes, ST elevation, and T-wave inversion. *X*-ray appearances suggestive of pulmonary vascular congestion or ventricular aneurysm and the cardio-thoracic ratio were specially noted.

Clinical examinations which included electrocardiographic and *x*-ray observations were made on discharge from hospital and at three monthly intervals thereafter. On these occasions information was collected on the following items:

Incidence and nature of haemorrhages or other complications.

Employment status.

Angina and dyspnoea graded thus:

O, None.

I, On severe exertion.

II, On normal activity.

III, On less than normal activity.

IV, Total incapacity.

Symptoms and signs of acute coronary insufficiency, or left ventricular failure.

Intermittent claudication.

Thrombo-embolic phenomena.

Diabetes.

Development of frozen shoulder syndrome.

Laboratory Control

Because of its widespread use, the unmodified one-stage "prothrombin" time test was used at all the participating centres. A level of two to two and a half times the control value was the aim of therapy. To ensure that the method was similar at all centres an instruction sheet was circulated before the trial. No rigid standardization of technique was attempted, but the same general pattern of test was used by all centres. To make certain that there were no gross deviations in results between the centres 16 samples were sent to them between September, 1956, and March, 1958. The results showed reasonable agreement, and the samples of citrated plasma showed remarkably little deterioration in the post. Twelve centres returned results for most of the specimens sent, and, of these, three centres returned slightly high results, three centres slightly low results, and from six centres average results were obtained. The results from individual centres were reasonably consistent; in other words a centre from which high results were obtained always had rather high results. A working sheet giving phenindione dosage and "prothrombin" times on each visit was kept for every patient.

Both groups were asked to attend regularly at intervals of one to three weeks for assessment, including venepuncture for biochemical tests. All patients were given cards stating that they were receiving anticoagulants and were instructed to hand these cards to their medical or dental attendant if they needed operations. In such an event, the surgeons concerned could refer to the centre for advice on the dosages of anticoagulants being given, the current "prothrombin"-time levels and the amount of vitamin K_1 required to prevent serious bleeding. For the low-dosage group no vitamin K_1 was required.

Withdrawals from the Trial

During surgical and medical emergencies which interfered with the regular dosage levels given, the patient was temporarily withdrawn from the trial; but on recovery he was replaced in the same dosage group as before the emergency. If a further infarction took place the patient was treated as the physician directed for up to 42 days. Then, unless a deterioration in his general condition necessitated a complete withdrawal from the trial, he was returned to his previous group.

Because of the important risk of selective withdrawal obscuring the true relative experience of the two series, the cause of each withdrawal was carefully recorded and a strenuous attempt made to discover the subsequent fate of those who were thus removed from the trial.

Detailed records were kept of every recurrence of infarction whether fatal or not; the clinical pattern of the attack, electrocardiographic evidence when available, and the certified cause of death were all noted. When a necropsy was performed the pathologist was asked to report his findings on a standard form. If no necropsy was performed—and this was true in the majority of cases—the cause of death given on the death certificate was recorded.

Assessment of Results

Although the clinician had no part in the allocation of the patients to types of treatment, he had to know the treatment being given so that he could regulate the dosage in the light of clinical and laboratory data. Since the main criteria of the result of treatment—namely, infarction and death—were objective, personal bias in assessment was not likely to disturb the broad pattern. The other features of circulatory disorder regularly recorded, such as claudication or thrombo-embolic phenomena and the graded assessment of angina or dyspnoea, could be used as ancillary measures of the effects of the continued administration of phenindione.

SUMMARY OF RESULTS

The success of the allocation procedure in ensuring equality between the two groups can be tested, as in Table I, by comparing the age and sex distribution of the patients randomly allotted to the two series. The differences found are small and within the limits of sampling variation. Table II shows that in other respects likely to be material the two series are alike. Since the initial stage of the allocation of patients was a grouping according to the number of previous infarcts and the ancillary forms of treatment in each hospital were identical, most, if not all, of the major sources of variation in outcome have thus been effectively taken into account. Comparison between the series can thus be directly made without adjustment or standardization for factors such as age or sex.

TABLE I.—*Age and Sex Distribution of Comparative Series*

Age	Low Dosage				High Dosage			
	Male		Female		Male		Female	
	No.	%	No.	%	No.	%	No.	%
40–44	11	7	1	4	15	9	1	3
45–54	58	36	4	14	58	35	5	17
55–64	68	43	18	64	74	45	17	57
65–69	23	14	5	18	18	11	7	23
Total	160	100	28	100	165	100	30	100

TABLE II.—*Previous History of Patients Allocated to Low-dosage and High-dosage Regimes*

Condition	Low Dosage Patients		High Dosage Patients	
	No.	%	No.	%
Angina	107	58	107	56
Claudication	10	5	19	10
Diabetes	9	5	4	2

TABLE III.—*Deaths and Withdrawals in Two Series According to Previous Infarct History*

No. of Previous Infarcts		Withdrawals		Deaths		Total No. of Patients
		No.	%	No.	%	
0	Low dosage	16	11	25	16	153
	High ,,	15	9	18	11	160
1	Low ,,	6	21	4	14	29
	High ,,	7	24	3	10	29
2	Low ,,	1	17	2	33	6
	High ,,	2	33	1	17	6
Total	Low ,,	23	12	31	17	188
	High ,,	24	12	22	11	195

TABLE IV.—*Cause and Fate of Withdrawals*

	No. of Patients	No. Followed Up	No. of C.V. Deaths	No. of Deaths All Causes
Low Dosage				
Severe cardiac infarcts	9	9	0	0
Pulmonary embolism	1	1	1	1
Cardiac failure	4	4	2	2
Peptic ulcer or dyspepsia	2	2	0	0
Pulmonary tuberculosis	1	1	0	0
Sensitivity to phenindione	2	2	0	0
Failures in co-operation	4	4	1	1
Total	23	23	4	4
High Dosage				
Cerebrovascular accident	3	3	0	0
Cardiac failure	3	3	2	2
Peptic ulcer (2 with haematemesis)	6	6	1	1
Traumatic episodes (with bleeding)	3	3	0	1*
Other disorders (associated with bleeding)	3	3	1	1
Failures in co-operation	6	5	1	1
Total	24	23	5	6

* Patient with fractured skull died shortly after withdrawal.

The basic results in terms of death, survival, or withdrawal are set out in Table III, where it is clear that the death rate has been higher in the low dosage group, though this divergence could have occurred by chance. Withdrawals, for all reasons, were equally frequent in the two series. Since the selective withdrawal of the more seriously ill in either series may affect the apparent case fatality rate, the reasons for such removals are crucial in such comparisons. They are given in Table IV and they fall into several categories.

Experience of Patients Withdrawn from the Trial

Of the 188 patients receiving low doses 23 were withdrawn from the trial. Nine patients had recurrent infarcts with such a marked deterioration in their condition that their physicians removed them from the prescribed trial regime and treated them in a more flexible manner. Of the remainder the medical reasons for withdrawal were: pulmonary embolism (one patient), signs or symptoms of peptic ulceration (two patients), skin signs of sensitivity (two patients), pulmonary tuberculosis (one patient), cardiac failure (four patients).

Of the 195 patients receiving high doses, 24 were withdrawn. Five patients developed conditions which were associated with bleeding (one leaking aneurysm of the abdominal aorta, one haematuria with retention of urine, one haemorrhoids and two haematemeses. Three patients sustained injuries or underwent operations which necessitated prolonged withdrawal and ultimate removal from the trial (one amputation of foot, one fractured skull and one fall with severe haematoma of loin). Three patients were presumed to have had cerebrovascular accidents; one had a subdural haematoma treated surgically; one developed a right external rectus palsy considered to be due to a cerebral thrombosis, and one was diagnosed as subarachnoid haemorrhage; all three patients survived. Four other patients were withdrawn for signs or symptoms of peptic ulceration, and three because of cardiac failure.

The frequency of failure or inability to carry on in the trial because of personal or transport difficulties was similar in the two groups (four and six patients respectively).

The fate after withdrawal of 23 of the patients given low doses and 23 receiving high doses was discovered by local inquiry. From Table IV it is clear that the death rates from cardiovascular disease among these withdrawals from both groups of patients are not very different. Because of the problem of changing treatment these results in patients withdrawn from the trial cannot be rigorously assessed. For these reasons, only the outcome during observation on either dosage regime before withdrawal is considered here.

Criteria of Therapeutic Achievement

The main criterion of the practical success or failure of the two dosage regimes is the death rate from all causes (cardiovascular and other) among those admitted to the trial, whether later withdrawn or not. Next in importance is the frequency of infarction which has necessitated a permanent removal from the trial and of infarction which was not serious enough to warrant such withdrawal. Finally, it is important to know if there is any difference in physical status of the survivors,

as judged by working capacity, breathlessness, or anginal pain. Against any such benefits must be put any serious complications associated with high dosage anticoagulant therapy. Differences between the two dosage levels in each of these respects may appear only in certain subgroups of the patients concerned and at certain stages in the follow-up period. The analysis of the clinical data has therefore been largely concerned with these various aspects of the experience of the two series.

Deaths During Supervision in Trial

Post mortem examinations were carried out in only 9 out of the 31 deaths reported among patients receiving low dosage and in 4 out of 22 of those given high dosage.

Of the 31 deaths in patients receiving the low dosage, 28 were ascribed to recurrent cardiac infarction resulting in acute heart failure or sudden collapse and death. One patient died after sudden collapse but no fresh infarct was found at post mortem examination and the cause of death in one patient was not recorded. One of this series of patients died from cerebral embolism. Among the 22 deaths in patients given high dosage, only one patient was certified as dying from cerebral haemorrhage; and of the others, three died from congestive failure without clinical evidence of further infarction. Death in the remaining 18 patients apparently followed infarction.

Table V shows that in males there are more deaths in the low than in the high-dosage group, but the difference does not reach the 5% level of significance. The difference is present both above and below the age of 55, but it is slightly greater in younger than in older age groups. Again neither difference reaches the 5% level of statistical significance. In females the death rate is slightly higher in the high dosage group, but the numbers are too small to be sure that a difference as large as that observed in the males does not exist.

TABLE V.—*Deaths and Fatality Rates Observed in the Two Treatment Groups*

Age	Males			Females		
	No. of Patients	Deaths		No. of Patients	Deaths	
		No.	%		No.	%
Low Dosage						
40–44 ..	11	3	27	1	—	—
45–54 ..	58	11	19	4	—	—
55–64 ..	68	8	12	18	3	17
65–69 ..	23	6	26	5	—	
Total ..	160	28	18	28	3	11
High Dosage						
40–44 ..	15	1	7	1	1	100
45–54 ..	58	6	10	5	—	
55–64 ..	74	9	12	17	3	18
65–69 ..	18	1	6	7	1	14
Total ..	165	17	10	30	5	17

Although the death rate is higher in those with a history of more than one previous infarct, the high dosage regime seems, from Table III, to have had some beneficial effect in both the other subgroups. The difference between infarct groups is, however, negligible. In the analysis of the mortality experience, therefore, the previous history has been ignored.

Infarct Experience in Relation to Sex, Age, and Treatment

The numbers of patients who were removed from the trial because of serious infarcts or at the onset of signs of impending cardiac failure are too small to make their separate analysis useful. When combined with the deaths, as in Table VI, there emerges a clear suggestion that failures in prophylaxis or treatment as thus defined are significantly less among males. Under the age of 55, the eight male deaths or removals in the high dosage group are significantly lower than the corresponding 19 in the low dosage series.

Infarction which may or may not be serious enough to cause removal from the trial is of particular significance from both the practical and the theoretical point of view. Table VII shows the frequency of such events as the total number of infarcts among the members of each age-sex group and the infarct rate per 100 person-months of exposure. The pattern already observed in the death and other wastage tabulations is more clearly apparent in this summary of the infarct experience. As before, the females in so far as the small numbers permit judgment show little beneficial response to high doses of anticoagulants. Among the males there is still a suggestion of a better result among the younger men, under the age of 55. The high dosage group above and below the age of 55 suffered infarcts at rates respectively one-half and one-fifth of the rate suffered by the corresponding low dosage patients—disparities between high- and low-dose groups which are in neither instance likely to have arisen by chance. On the other hand, this difference in result between the two male age groups could be fortuitous.

TABLE VI.—*Deaths, Severe Infarcts, and Cardiac Failures Causing Removal from Trial in Comparative Series*

Age	Males			Females		
	No. of Patients	Deaths and Removals		No. of Patients	Deaths and Removals	
		No.	%		No.	%
Low Dosage						
40–44 ..	11	3	27	1	—	—
45–54 ..	58	16	28	4	1	25
55–64 ..	68	9	13	18	5	28
65–69 ..	23	10	43	5	0	—
Total ..	160	38	24	28	6	21
High Dosage						
40–44 ..	15	1	7	1	1	100
45–54 ..	58	7	12	5	—	—
55–64 ..	74	10	14	17	4	24
65–69 ..	18	1	16	7	1	14
Total ..	165	19	12	30	6	20

TABLE VII.—*Rate of Subsequent Infarcts in the Two Treatment Groups*

Age	Males			Females		
	No. of Patients	No. of Infarcts	Infarcts per 100 Person Months	No. of Patients	No. of Infarcts	Infarcts per 100 Person Months
Low Dosage						
40–44 ..	11	3	2·1	1	—	
45–54 ..	58	30	3·5	4	1	1·3
55–64 ..	68	13	1·2	18	5	2·1
65–69 ..	23	8	2·4	5	—	—
Total ..	160	54	2·2	28	6	1·5
High Dosage						
40–44 ..	15	1	0·4	1	1	33·3
45–54 ..	58	7	0·7	5	—	—
55–64 ..	74	7	0·6	17	5	1·9
65–69 ..	18	2	0·9	7	1	0·9
Total ..	165	17	0·6	30	7	1·4

TABLE VIII.—*Subsequent Myocardial Infarction in Relation to Previous Infarct History*

	History of No Previous Infarct				History of One or More Previous Infarcts			
	Low Dosage		High Dosage		Low Dosage		High Dosage	
	Male	Female	Male	Female	Male	Female	Male	Female
No. of infarcts	39	5	14	5	15	1	3	2
,, ,, patients	132	21	133	27	28	7	32	3
Person-months of exposure	2,006	330	2,205	388	453	72	534	51
Infarct rate %	29·5	23·8	10·5	18·5	53·6	14·3	9·4	66·7
Rate/100 person-months of exposure	1·9	1·5	0·6	1·3	3·3	1·4	0·6	3·9

TABLE IX.—*Timing and Frequency of Deaths, Withdrawals, and Fresh Infarcts among Male Patients*

Period since Admission (in Months)	Low Dosage							High Dosage						
	Man-mths of Exposure	Deaths		Withdrawals		Infarcts		Man-mths of Exposure	Deaths		Withdrawals		Infarcts	
		No.	Rate/100 Man-mths Exposure	No.	Rate/100 Man-mths Exposure	No.	Rate/100 Man-mths Exposure		No.	Rate/100 Man-mths Exposure	No.	Rate/100 Man-mths Exposure	No.	Rate/100 Man-mths Exposure
<3	451	12	2·7	3	0·7	18	4·0	481	4	0·8	6	1·3	5	1·0
3–	418	7	1·7	3	0·7	10	2·4	456	5	1·1	1	0·2	5	1·1
6–	370	3	0·8	4	1·1	8	2·2	424	2	0·5	4	0·9	2	0·5
9–	331	—	—	2	0·6	4	1·2	355	3	0·8	5	1·4	3	0·8
12–	269	1	0·4	1	0·4	5	1·9	290	—	—	—	—	1	0·3
15–	206	2	1·0	1	0·5	3	1·5	245	—	—	—	—	—	—
18–	162	1	0·6	1	0·6	2	1·2	189	—	—	4	2·1	—	—
21–	110	1	0·9	—	—	2	1·8	128	—	—	—	—	1	0·8
24–	63	1	1·5	1	1·5	1	1·5	83	1	1·2	1	1·2	—	—
27–	40	—	—	1	2·5	1	2·5	54	1	1·9	1	1·9	—	—
30–	26	—	—	—	—	—	—	26	1	3·8	—	—	—	—
33–35	11	—	—	—	—	—	—	8	—	—	—	—	—	—
Total ..	2,459	28	1·1	17	0·7	54	2·2	2,739	17	0·6	22	0·8	17	0·6

Relevance of Previous Infarct History

Table VIII contrasts the difference in reinfarction rates, according to the dosage received, among patients who had a history of either none or one or more infarcts before the infarct leading to their admission to the trial. There is a suggestion that, for males alone, the disparity in reinfarction rate associated with therapy is greater among those with one or more previous infarcts; but the difference is not numerically important enough to affect the general conclusions from the previous tables.

Time Distribution of Death and Infarction

The timing of death or reinfarction may be as important as their frequency in the assessment of results in a trial like this. Table IX summarizes for males, within three-month periods after admission to the trial, the time distribution of death, withdrawal for all reasons, and infarction. Within each time period the total number of months under observation in the trial is calculated for all the members still surviving for any part of the period. The risk, for example, of dying whilst under observation, within each period, is then expressed as a rate per 100 person-months of exposure. (Thus, 12 deaths among 160 men observed for a total of 451 months give a rate of 2.7 per 100 man-months of exposure.) From this table it is obvious that the difference in the death rate is appreciable only in the first three months of the follow-up period. The disparity in the infarct rate, on the other hand, is fairly consistently present even during the second year of follow-up.

It seemed possible that the increased liability to death from cardiac infarct in those receiving the low doses of phenindione might be due to the sudden withdrawal of anticoagulant treatment. To investigate this the deaths in both the low- and the high-dosage groups are shown in Table X week by week during the first four weeks, and for the subsequent two months, after admission to the trial. It will be seen that there is no striking tendency for the deaths in the low-dosage series to occur in the first two weeks, although all but three of the series are recorded as having previously received anticoagulant therapy. The fate of those withdrawn from the trial had the same import; only one patient died from congestive failure within one month of stopping the high-dosage regime.

TABLE X.—*Time of Occurrence of Deaths in First Three Months After Admission to Trial*

Weeks	Low Dosage		High Dosage	
	Males	Females	Males	Females
<1 ..	1	—	—	—
1– ..	1	—	1	1
2– ..	3	—	—	—
3– ..	2	1	1	—
4– ..	2	—	1	—
8–12 ..	3	1	1	1
	12	2	4	2

TABLE XI.—*Occupational and Physical Status of Survivors (Males)*

Year of Follow-up	No. Survivors		No. Employed				No. Without Angina				No. Without Dyspnoea			
	Low Dosage	High Dosage	Low Dosage	% Surv.	High Dosage	% Surv.	Low Dosage	% Surv.	High Dosage	% Surv.	Low Dosage	% Surv.	High Dosage	% Surv.
1	23	30	13	57	26	87	12	52	18	60	15	65	22	73
2	68	67	48	71	55	82	37	54	45	67	43	63	44	66
3	24	29	21	88	23	79	11	46	18	67	19	79	17	59
Total ..	115	126	82	71	104	83	60	52	81	64	77	67	83	66

Condition of Survivors

The occupational and physical status of male patients who have survived and had not been withdrawn from the trial is described in Table XI. Here the indices used are a return to work and the absence of angina or dyspnoea at the time of the last routine clinical examination. The rates for occupational recovery and freedom from anginal pain agree in suggesting a small superiority among the men who were on the high-dosage levels. The data on dyspnoea are equivocal. Against this favourable result must be set the reporting of left ventricular failure in four and acute coronary insufficiency in two of the surviving patients on high dosage therapy. None of the other series was thus affected. "Frozen shoulder" and claudication were recorded relatively seldom and with equal frequency in the two series. No thromboembolic phenomena were reported among the survivors in either series.

Risks of High Dose Anticoagulant Therapy

The risks of high dosage anticoagulant administration are evident in the finding that during the follow-up period 48 haemorrhages of varying degrees of severity in several sites in the body were reported in the histories of all patients thus treated. Only eight such incidents were recorded in the low dosage series. As noted in Table IV, there were 15 withdrawals from the high dosage group because of haemorrhage or the risk of haemorrhage. There was one report of bruising of elbow and one of minor haematemesis among those ultimately withdrawn because of infarcts from the low dosage series.

Among the patients dying while on high dosage, one death followed cerebral haemorrhage while of those on low dosage embolism was considered a likely complication of the terminal illness in three patients.

DISCUSSION

The two previous trials in which apparently adequate control series have been provided differ considerably in their results. Over a ten-year period of observation in Washington, D.C., Manchester (1957) found that the average death rate among his anticoagulant-treated patients was one-sixth of that in a concurrent series of patients given tablets containing ascorbic acid. Bjerkelund (1957) in Oslo, on the other hand, reported a reduction in mortality by only about a third; and this was confined to the first year after admission to his trial of long-term anticoagulant therapy. Our results in respect of mortality are close to those in the Norwegian study. The incidence rates of both re-infarction and death in Manchester's series of patients not given anticoagulant therapy are lower than in either Bjerkelund's or our studies. The withdrawal rates for all reasons also appear to be higher in the American study and it seems likely that these infarction and death rates have been based on a survivor population whose general cardiac condition was less serious than that of the patients included in either of the European trials.

In both the Norwegian and the British studies the risk of death and cardiac failure or reinfarction is reduced significantly in younger males in the early stage of follow-up. Moreover, the condition of the survivors, measured in terms of working capacity and freedom from angina, is rather better in those given high doses of anticoagulant drugs. Because of the difficulty in assessing dyspnoea, the discordant results obtained are unlikely to be of much significance.

In our data, the benefits of therapy as revealed by a lowering in the infarction rate appear most clearly in those groups, such as younger male patients and those with more than one previous infarct, where the risk of recurrent infarct is high. Bjerkelund also found that the benefit was greater in younger males. In our small experience among women no benefits as thus assessed were seen.

By reducing the incidence of cardiac complications associated with thrombosis, anticoagulant therapy may preserve the lives of patients with serious heart damage. The four patients in the high-dosage group who survived without a fresh infarct, in spite of the presence of ventricular failure, may be examples of such an event. Since the incidence of death and withdrawals for cardiac failure in older patients is little affected it would seem that the value of a treatment theoretically designed to inhibit thrombosis is likely to be severely limited in patients with severe cardiac damage.

The results agree with Bjerkelund's suggestion that benefit in terms of deaths is most evident in the first few months after recovery from the presenting infarct, and with Manchester's view that the reduction of the infarction rate continues for a longer time. Although the groups of patients admitted to the two forms of therapy were initially comparable, the removal by death and the selective removal of the more seriously ill in the first year produces increasing disparity; and that makes the results progressively more difficult to interpret. At the end of the first year the high-dosage series presumably includes a number of patients whose cardiac condition is such that they would have died without the protection of an effective anticoagulant. Strictly speaking, the subsequent fate of patients on high dosage cannot be fairly compared with that of the selected survivors among those given the low dosage. Any reduction in the infarct rate associated with continued anticoagulant therapy beyond the first year or two must therefore underestimate the benefit of such treatment.

With the degree of clinical and laboratory control exercised in this study, haemorrhagic episodes had few dangerous results. Any excess in cerebrovascular accidents among those on high doses was almost balanced by embolic phenomena in chest or brain in those under low-dosage regimes.

A subsidiary aim of this trial was to throw light on the possible factors concerned in producing cardiac infarction. It is difficult to draw any conclusions about this from our results. Thus it is not yet known whether the beneficial effects of phenindione therapy, which taken severally seem small but taken in bulk seem real enough, are exerted through the clotting mechanism. There is a suggestion from our figures, but none from Bjerkelund's, that this effect is greater in males than in females. We mention these points, not because of the cogency of our evidence, but in the hope that further work may clarify what is still obscure.

The conclusions derived from this preliminary analysis must be tentative. The strict criteria adopted in this study exclude about two-thirds* of patients admitted to hospital, diagnosed and treated as cases of cardiac infarction. Our conclusions apply only to the type of patients selected. But it appears that phenindione

*Among 1,035 patients admitted to eight of the participating centres with the diagnosis of myocardial infarction, 300 were included in the trial.

administered continuously in the conditions of this trial can make a useful, if limited, contribution in the after-care of patients who have recovered from the acute phase of myocardial infarction.

SUMMARY AND CONCLUSIONS

There is a clear need for a sound assessment of the balance of risks and benefits derived from long-term continuous anticoagulant administration in the care of patients who have survived acute myocardial infarction. A controlled trial has been carried out to compare the clinical progress of patients given doses of phenindione large enough to double the one-stage "prothrombin" time (and thus effectively interfere with coagulation) with the experience of a similar series of patients given tablets containing only 1 mg. of phenindione.

The 383 patients who had recovered from the acute phase of a cardiac infarction of defined severity were classified according to their previous infarct history and allocated at random, within each hospital centre, to these high and low dosage series. Both groups of patients were seen at regular intervals of about two to three weeks and clinically assessed more fully by *x*-ray and electrocardiographic methods every three months. Laboratory control was maintained by Quick's test of the one-stage "prothrombin" times, and in the high dosage series the amount of drug administered was adjusted to ensure a level of two to two and a half times the control value.

The reasons for withdrawal from the trial, whether physical, domestic, or personal, were noted for each series.

Three indices of the effectiveness of the regimes were used: (i) death from all causes, from cardiovascular disease in general and from recurrent myocardial infarction in particular; (ii) frequency of myocardial re-infarction of varying degrees of severity; and (iii) subsidiary data on return to work and the presence of anginal pain or dyspnoea at the time of the last examination.

Particular note was made of all incidents irrespective of severity, such as embolism and haemorrhage, which might be affected by anticoagulant therapy.

Comparisons were made between the outcome in different subgroups of patients and at different stages of the follow-up period which ranged up to a maximum of three years from the date of admission. The analysis showed that:

1. Although the death rate was higher in the low-dosage series, there is just the possibility that the difference could have occurred by chance. No difference was apparent in females, but the numbers were too small to exclude such a difference.

2. When the infarcts serious enough to cause permanent withdrawal from the trial were added to deaths as a combined index of prophylactic failure there was a significant reduction in their frequency among the males receiving the high doses; and there was a suggestion of a better result in males under the age of 55.

3. The same trends appear even more clearly when the total reinfarction rate is used as the basis of comparison. Under the age of 55, males on high doses suffered recurrent infarctions at only one-fifth of the rate of those on low dosage, and over that age the rate is halved by high dosage. These differences are statistically significant.

4. The proportionate reduction in the risk of reinfarction achieved by the high-dosage regime is slightly greater among patients with a previous history of one or more infarcts, but the difference is not statistically significant.

5. The difference in the death rate is most evident in the first six months of the follow-up period, but the disparity in the reinfarction rate is maintained for at least two years of the follow-up period.

6. More men given the higher doses returned to work during the period and they were more often free from angina.

7. There were 15 withdrawals from the high-dosage series because of the onset of conditions actively or potentially associated with haemorrhage. Four major cerebrovascular accidents—three causing withdrawal and one death—were reported among the high-dosage series. Only one patient on low dosage suffered a cerebral haemorrhage, but embolism was a major complicating feature in the terminal illness of three of them. There were 48 minor haemorrhagic incidents in the high-dosage group compared with eight among those on the low dosage.

These results have been compared with those in two similar previous studies. The close agreement in many respects with one of these clinical trials is discussed and the implications, aetiological and therapeutic, are considered.

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The expectation of working life of a man differs from his expectation of life because various factors, of which the chief is ill-health, can incapacitate him without killing him. The Ministry of Labour and National Service has now published life tables and working-life tables for males in Great Britain for the years 1955 and 1931. The expectation of working life at any particular age is the number of years at which, on certain assumptions, half the people who have reached that age and are working will no longer be at work because of death or retirement. Another way of looking at it is to say that it is the average number of years for which people who have attained any specified age will continue to work after that age. For example, in 1955 the expectation of working life of British males at age 20 was 43.6 years, and at age 40 it was 25.0 years. These figures differ surprisingly little from those for 1931, when the expectation of working life at age 20 was 42.1 years and at age 40 was 24.8 years. As this volume points out, such tables do not purport to show what will necessarily happen in the future. They express the experience of a past period, though, despite this, they can give guidance of practical use. The title of this volume is *The Length of Working Life of Males in Great Britain* (H.M.S.O., 3s. 6d. net).

AETIOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS

BY

HENRY MILLER, M.D., F.R.C.P.
Physician

AND

KURT SCHAPIRA,* M.B.
Research Fellow

From the Neurological Department, Royal Victoria Infirmary, and the Department of Medicine, the Medical School, King's College, Newcastle upon Tyne

PART II†

The essential clue to the causation of multiple sclerosis may be lacking amongst the observations outlined in Part I, and may await some apparently unconnected advance in another field of medicine, just as subacute combined degeneration and kernicterus were clarified by new haematological knowledge, or Wilson's disease by studies of copper metabolism. It is also possible that more convincing evidence than hitherto may be forthcoming to link the occurrence of the disease with *tuberculosis* (Ahringsmann, 1949–50), high *dietary fat* intake (Swank, 1953), or the geographical distribution of *heavy metals* or *trace elements* (Campbell *et al.*, 1947, 1950); that the roles of *microthrombosis* (Putnam and Alexander, 1939), *vasospasm* (Brickner, 1950), or *red-cell sludging* (Roizin et al., 1953) may prove to be more than incidental; or that the recent experimental production of demyelination by such agents as *potassium cyanide, sodium azide,* or *anoxia* may be more relevant to the human disease than appears at first sight.

Present Position

In general, however—and with the reservation that our ideas and discussions are relevant only within the framework of contemporary conceptions, and doubtless reflect current preoccupations every bit as dated as Cruveilhier's "insensible perspiration"—it would appear that the main controversy rests between two concepts. The first is that the disease is caused by a specific infective agent, most probably a virus; the second is that it represents one clinical form of a characteristic pathological response in the nervous system, variable in localization and tempo, and in some way related to a disturbance in the balance of immunity and allergy.

In our view the clinical features, natural history, and epidemiology of multiple sclerosis do not specially favour a direct origin in infection by a specific virus, but the possibility certainly cannot be excluded and clearly merits the continued application of new virological techniques.

The unitary allergic hypothesis of Pette and of Ferraro relates to pathogenesis rather than to aetiology, and indeed the two concepts of the disease are not necessarily exclusive. The allergic view is based on the similarities that exist between multiple sclerosis, acute disseminated encephalomyelitis, and experimental allergic encephalomyelitis. The analogous nature of the last two syndromes is widely accepted. The gist of the problem concerns the relationship between acute disseminated encephalomyelitis and the uniquely human chronic disease multiple sclerosis.

To discuss such a relationship demands some definition of terms. The reluctance of most writers on the subject to define multiple sclerosis, and the studied vagueness of such definitions as have been attempted, immediately arouse an uneasy suspicion that some of the argument in the literature may be about words rather than things.

If we were to synthesize a brief clinical definition of multiple sclerosis from current textbooks it would depict a chronic relapsing disease of the nervous system, of unknown aetiology, chiefly affecting young adults, initially intermittent but subsequently characterized by progressive disability, and terminating after a period of years in severe incapacity and death. An acute encephalomyelitic illness, on the other hand, is generally regarded as an isolated self-limited episode, usually following a frank infection, more sudden and catastrophic in onset than the chronic disorder, and either immediately fatal or more often leading to rapid and lasting recovery.

Such definitions and the orthodox formulation which they present are implicit in most of the current literature. How far do they correspond with the facts? The senior author of the present paper is one of many who have in the past attempted to explore and define the differences between these two symptoms, but it must be admitted that this traditional position has been rendered more insecure by the clinical and pathological evidence of the last few years, and in particular by the definitive description of encephalomyelitis following inoculation against rabies to which attention has already been directed. Virchow's aphorism that system and authority are the greatest enemies of medical advance is not entirely inappropriate in this context, and increased understanding of these diseases may depend less on the acquisition of new facts than on the rearrangement into new patterns of facts already familiar.

Informed appraisal of the histopathological issues already briefly outlined is beyond our competence; the remainder of this discussion is devoted to clinical considerations relevant to this relationship. Histopathological appearances are often regarded as the final court of appeal in issues of this kind, but in the present instance such limitation does not involve great sacrifice. The contribution of histopathology in human cases relates only to terminal findings; it is often uncertain how far atypical appearances in encephalomyelitis indicate different reactions or merely different stages in a single process; and, in any case, only the clinical history will indicate the *development* of the lesion and reveal possible aetiological factors. The clinical aspects discussed are limited to three headings—symptomatology, natural history and prognosis, and aetiological background.

Symptomatology

With regard to symptomatology, McAlpine's (1931) classical observations on the differentiation of these two groups of cases are constantly employed as guides to the difficult matter of prognosis in individual cases, and they remain generally valid: the more explosive the onset of symptoms in an equivocal acute neurological

*Holding a Research Fellowship in Neurology financed by the North-east Multiple Sclerosis Trust and also supported by the Board of Governors of the United Newcastle upon Tyne Hospitals.

†The first part of this article appeared in last week's issue.

illness of this type, the greater would appear to be the chance of its rapid and lasting resolution. In fact, however, the symptomatic outlines of both these syndromes are blurred. There is no single clinical feature encountered in cases diagnosed as multiple sclerosis which cannot be duplicated in encephalomyelitis, and vice versa. The literature bears ample witness to the fallibility of expert diagnosis in this field, and our personal experience of more than a thousand patients with multiple sclerosis and of close on a hundred cases diagnosed as acute disseminated encephalomyelitis confirms the aphorism of the American neurologist who said that the only typical feature of multiple sclerosis was that it was always atypical.

Amongst particular symptoms generally regarded as of diagnostic value one example will suffice. *Clouding of consciousness* is a sign of encephalitic illness so classical that a semantic difficulty arises: almost any neurological illness characterized by stupor tends to be so labelled at some stage. In acute disseminated encephalitis as in other cerebral illnesses the degree of impairment of consciousness is closely related to prognosis, and is an index both of the severity of the lesion and of its generalized nature. In contrast, mental clouding more rarely results from the less acute and focal lesions of multiple sclerosis. In fact, however, a frankly encephalitic syndrome not only may initiate multiple sclerosis, but may recur during its course.

Case 138.—A previously healthy woman of 23, two months pregnant, was admitted to hospital in April, 1956, as a case of undiagnosed fever of six days' duration, characterized by intense headache, vomiting, marked drowsiness, photophobia, and neck stiffness. An equivocal left plantar response was the only focal sign and the spinal fluid was normal. Within seven days the temperature fell from 102.5° F. (39.2° C.) to normal, revealing gross ataxia as the only abnormal finding. The paucity of objective neurological signs was such that one experienced observer suggested that the fever might have been simulated. She was discharged undiagnosed a week later, with very slight unsteadiness of gait as the only sign. After a further month, insidious weakness of the left leg developed, with a definite extensor plantar response. Euphoria became evident, followed within six weeks by an acute right retrobulbar neuritis. Almost complete recovery once more ensued; but nine months later, in April, 1957, she developed a further acute neurological illness characterized by stupor, disorientation (she could not recognize her husband), and gross cerebellar ataxia. Rapid recovery over the course of 14 days left some euphoria, ataxia of gait, a left extensor plantar response, and pallor of the right optic disk, as the only abnormal findings.

If a further symptomatological illustration is required it is furnished by Devic's syndrome of *neuromyelitis optica*, dependent on simultaneous or successive demyelinating lesions in the optic nerves and spinal cord. Brain (1951) has reported this condition as a sequel of measles. Scott (1952) has drawn attention to partial syndromes of this nature and to their generally favourable prognosis, while Miller and Evans (1953) have reported a benign recurrent form. Finally its occurrence as a manifestation of typical multiple sclerosis is now well authenticated. It is true that neither an identical localization of signs nor a similar basis in demyelination necessarily implies aetiological unity. Nor, on the other hand, does the variable prognosis of neuromyelitis optica constitute in itself a valid basis for postulating differences in the essential pathology of this relatively stereotyped syndrome.

Natural History and Prognosis

Critical consideration of the natural history in patients diagnosed as suffering from multiple sclerosis and from acute disseminated encephalomyelitis yields similarly equivocal results. The course of classical multiple sclerosis is initially remittent, advancing to a later stage of progressive deterioration. However, remission may be classical, but it is by no means invariable: more than 10% of cases diagnosed as multiple sclerosis deteriorate progressively without any interval of arrest or improvement. At the other extreme is an appreciable proportion of patients, well recognized since the time of Marie and familiar to every neurologist, in whom the disease runs an essentially benign course. Deterioration may be barely perceptible over decades, while in some cases disability and signs become quite static.

Such illnesses tend to run true to type, and a favourable prognosis is especially common where the onset has been mild or monosymptomatic: the majority of Hyllested's (1950) series of patients affected by acute retrobulbar neuritis either remained well or were only trivially disabled by minor evidence of multiple sclerosis nine to twenty-five years later. Nor are relapse and recurrence unknown among cases recorded as instances of acute disseminated encephalomyelitis, especially where the initial episode has followed the type of non-specific upper respiratory infection which results in less lasting immunity than in the case of an exanthem. Furthermore, a single encephalomyelitic episode may on occasion give rise to a non-progressive syndrome of residual disability with signs quite indistinguishable from those of established multiple sclerosis (Miller and Evans, 1953).

Aetiological Background

A convincing history of infective illness immediately preceding the onset of multiple sclerosis is less common than in the case of perivenous encephalomyelitis, but this may be partly due to the fact that the chronic disease so often develops insidiously that it may be difficult accurately to identify its beginning. However, such aetiological factors as can be defined in the natural history of multiple sclerosis seem to be of much the same kind as in acute disseminated encephalomyelitis. McAlpine and his colleagues (1955, Case 137) have indeed recorded one case in which an illness that subsequently declared itself as typical multiple sclerosis either followed or was initiated by neurological symptoms which developed after an attack of scarlet fever at the age of 10 years, and recurred in association with varicella at 17. The same authors have also reported the onset of the disease after various forms of vaccination. In this last connexion our experience parallels that of McAlpine.

Case 189.—Five years after an uneventful primary vaccination a previously healthy 23-year-old woman was revaccinated against smallpox. Within 48 hours she developed dragging of the left leg, clumsiness of the left hand, and dysuria. These symptoms cleared up in the course of a few months, but 12 months later, in 1946, she developed a left retrobulbar neuritis. In 1949 the right eye was similarly affected, and in 1953 the left. In 1956 she had an episode of precipitancy of micturition. Examination in July, 1957, revealed bilateral optic atrophy, some peripheral blunting of sensation in the lower limbs, absent abdominal reflexes, and a right extensor plantar response. Disability was minimal.

Case 313.—In 1942 a 22-year-old airman, who had received primary vaccination against smallpox and T.A.B./

T.T. inoculation six weeks previously without ill effect, was inoculated against yellow fever. This was followed within a matter of hours by progressive failure of vision in the left eye, in which he became almost blind within 72 hours; vision on the right was blurred. As he was on an overseas draft he was suspected of hysteria, and was admitted to hospital under police escort, where a severe left retrobulbar neuritis was discovered. There was no unequivocal evidence of involvement of the right eye. A year later, immediately after marriage and in relation to a period of fatigue and late hours, he developed a brief episode of right retrobulbar neuritis. Between 1944 and 1951 he had about a dozen recurrent episodes of more central involvement, with numbness on either side of the body (sometimes including the face), hemiparesis, and emotionalism. From 1951 until examination in November, 1957, there had been remission, with no acute exacerbations and little if any deterioration. At this time slight ataxia of gait, left optic atrophy, left intention tremor, absence of the abdominal responses, and some euphoria were the only positive findings, and disability was slight.

Case 77.—In June, 1955, at the age of 45, 26 years after a right facial palsy and 18 years after a transient diplopia, a reserve airman was secondarily vaccinated against smallpox and received a combined T.A.B./T.T. inoculation. Between 1941 and 1945 he had been inoculated with similar material on six occasions without ill effect. Within 12 hours of the injection in June, 1955, fever, rigors, blurred vision, and diplopia developed, and persisted for 48 hours. Two weeks later a second T.A.B./T.T. inoculation was followed by a similar but rather less severe disturbance. In February, 1956, he developed weakness of the right leg which cleared up in six weeks, and in June clumsiness of the right hand of sudden onset persisted for two weeks. In August, at the time of the Suez crisis, fever, blurring of vision, and difficulty in focusing on near objects followed a further T.A.B./T.T. inoculation. In November he was affected by a severe episode of vertigo. Examination in December revealed dysarthria, nystagmus to the left, right facial weakness, intention tremor of the left hand, and an absent right lower abdominal reflex. Disability was minimal.

Comment on Cases

We believe that there can be no reasonable doubt about the diagnosis of multiple sclerosis in these three cases, and that they are of considerable theoretical importance as indicating that the chronic disease can not only be exacerbated (Case 77) but also be initiated (Cases 189 and 313) by a variety of inoculations in which the incrimination of a common specific infective agent is highly improbable. This is especially so in Case 77, which recalls the exacerbation of pre-existing multiple sclerosis by successive injections of autogenous vaccine seen in Case 202 of McAlpine *et al.* (1955). It is of interest also in connexion with the cases of Bannwarth (1948) from the Germany Army, in which recurrent but self-limited neurological illnesses followed repeated inoculations of T.A.B. So far as Bannwarth's follow-up of these cases went, no relation to multiple sclerosis was suggested, the critical difference being *the absence of any neurological recurrences independent of further inoculation.*

Case 189 complements a previous paper (Miller, 1953) in which the usually excellent prognosis in patients surviving neurological complications of Jennerian vaccination was stressed. Twenty-seven cases were described, including eight in which involvement of the spinal cord occurred, either alone or as part of an encephalomyelitic picture. These cases were followed for periods varying from two to twelve years (the average follow-up being six and a half years), and in none had neurological symptoms recurred. The post-vaccinal case (No. 189) is drawn from the same service material, but in view of the fact that the condition would not be officially classified as an example of "neurological sequelae of vaccination" it may well be amongst a number of such instances lost sight of by a change of diagnosis to multiple sclerosis.

In Cases 189 and 313 there would appear to be no more reason to deny a genuine aetiological relationship between the inoculation and the subsequent development of multiple sclerosis than in the case of the acute self-limited neurological lesions following inoculation described by Miller and Stanton (1954). What gives these cases of multiple sclerosis their special character is a tendency to the subsequent occurrence of similar neurological episodes arising independently of any repetition of the original aetiological insult, and it is in this tendency to apparently spontaneous recrudescence that any special nature of the chronic disease would appear to consist.

It is noteworthy also that in each of the above three cases the multiple sclerosis was of a very mild type. It might be speculated either that the pathogenetic mechanism of the disease in these individuals was of a less active nature, or, conversely, that they possessed some power of resistance to the intensity and spread of the lesion such as has frequently been postulated in similarly benign cases. Whichever mechanism be involved, it seems conceivable that had they not encountered this particular exogenous insult to the nervous system they might have avoided the initiation of the pathological process which ended in the development of multiple sclerosis.

Conclusions

The practical usefulness of current classification as a rule-of-thumb guide to prognosis is beyond question; not even the most ardent monist would impugn the pragmatic value of clinical differentiation between most cases of post-measles encephalitis and most cases of multiple sclerosis. It is when we come to consider the nature of these disorders that the clinical evidence outlined in the previous sections of this paper lead us to question its ultimate validity. Neither clinical nor pathological considerations permit finality, but the unitary hypothesis of Pette and of Ferraro appears to us to do less violence to the facts than do the arbitrary and confident subdivisions which have gradually taken shape over the years from the gradual accretion of fragmentary clinical observations.

The unitary hypothesis visualizes a spectrum of demyelinating disease ranging from the most acute cases of frankly post-infective or post-vaccinal encephalitis or myelitis at one end of the scale to the insidious and remorselessly progressive chronic spinal form of multiple sclerosis with which we are familiar in middle-aged patients at the other. There are good reasons to include in such a spectrum also a number of other syndromes such as *acute haemorrhagic leuco-encephalitis* (almost certainly a manifestation of hypersensitivity) and *Schilder's disease* (now widely regarded as an analogue of multiple sclerosis), but such considerations are outside the scope of the present study.

The hypothesis postulates a common origin for this type of pathological reaction in some kind of hypersensitive disturbance, and on this reckoning the relation

between acute disseminated encephalomyelitis and multiple sclerosis might be compared with that between the acute disseminated exudative reaction of miliary tuberculosis and chronic remittent recrudescent fibroid phthisis—strikingly dissimilar syndromes of identical aetiology that owe their differences entirely to the subsequent interplay of the forces of immunity and allergy. Possibly the obscure condition of Boeck's sarcoidosis—where if there ever was a tubercle bacillus it has disappeared without trace, leaving only the ravages of its disintegration—provides an even more suggestive hint of the mechanisms which might operate in neuro-allergy.

In this view the whole concept of classical multiple sclerosis represents in essence an extrapolation made by applying certain arbitrary nosological criteria to a group of clinical phenomena not so subdivided in nature. In this way a semantic artifact has developed, growing both larger and vaguer over the years, but endowed with a spurious precision which fades on critical examination. It can hardly be denied that much of the confusion in this situation is a matter of terminology. A good deal of the argument—for example, on whether in some instances disseminated encephalomyelitis *turns into* multiple sclerosis, or whether the two acute illnesses are *different but indistinguishable*—is almost meaningless, and endows the idea of a disease-entity with a reality and an immutability strikingly at variance with Lord Cohen of Birkenhead's apt description of it as a "convenient conceptual label."

As we see it, what may be broadly termed the allergic hypothesis may be briefly developed in the following terms. The initial lesion in multiple sclerosis appears to be focal disseminated microscopic perivenous exudation and oedema. This is accompanied or followed by an inflammatory reaction of variable intensity at the same site, which is in turn succeeded there by the well-defined demyelination and glial proliferation typical of the established disease. The active margin of this characteristic lesion subsequently extends, either massively or by confluence, either insidiously or episodically, in a manner which appears at this stage to ignore vascular territories, and which suggests the possible diffusion of some demyelinating agent or process. Experimental evidence has shown that a somewhat analogous lesion can be provoked in animals without the participation of any infective agent, and apparently in the form of an antigen-antibody reaction resulting from tissue-sensitization. The initiating aetiological agent in this experimental disorder is the injection of sterile extracts of animal nervous tissue.

In the closely similar human clinical syndrome, acute disseminated encephalomyelitis, it is clear that either virus infection—for example, measles, varicella—or the injection of various sterile antigenic substances—for example vaccination—may play a similar aetiological part. In experimental encephalomyelitis and in the human disorder as it follows sterile inoculation there is good reason to believe that the initial perivenous lesion which is the first visible pathological sign of the disease represents in itself the larval manifestation of neural hypersensitivity. If for a moment we accept the hypothesis that multiple sclerosis may have a similar allergic pathogenesis, *the nature of the primary aetiological insult* which initiates the process of sensitization in the human disease still remains to be sought. In this instance also it seems to us probable that the initial perivenous exudation may represent merely the beginning of the secondary hypersensitive reaction, evidence of the true aetiological agent being buried in the past. Speculation on the nature of this primary aetiological factor is even less securely based than what has gone before, but both clinical evidence and historical considerations suggest that it may be non-specific, and that except in the occasional iatrogenic instances in which the disease has followed the deliberate introduction of antigenic substances into the human body it can best be tentatively regarded as a late sequel of various infective processes.

On the other hand, it is at any rate possible that the primary exudative lesion in the case of the human disease might in itself represent the point of attack of an initial infective agent, possibly of a viral nature: in herpes simplex we are familiar with a recurrent exudative reaction arising in ectodermal tissues which is strikingly and repeatedly potentiated by a wide variety of exogenous and endogenous factors such as infection, trauma, and emotional disturbance, in a manner not dissimilar to that seen in the case of multiple sclerosis. It is possible to envisage some similar recurring process in the central nervous system, each episode of which might reactivate a local process of tissue-sensitization releasing a further quantum of demyelinating fluid. The usefulness of so speculative an approach may well be questioned, and the last variant of the hypothesis castigated as seeking to combine the best of both worlds. On the whole the postulation of a specific virus, even as a link in the allergic hypothesis, is supported by less in the way of circumstantial evidence than a non-specific and multiple primary aetiology, though it has perhaps the advantage that it focuses attention on two possible avenues of investigation and of prophylactic or therapeutic interference—an infective aetiology and an allergic pathogenesis.

Indeed, the only excuse for a speculative hypothesis of this nature is that analysis must succeed synthesis in leading to observations or experiments which will provide evidence to confirm or refute it. In our view the allergic or immunological theory of multiple sclerosis, with all its loose ends and inadequacies, provides the most useful working hypothesis at present available from this point of view. In the pathological field the nature of the perivascular exudate, the problem of whether in fact this results from exudation or is formed *in situ*, and its relation to the increase in spinal fluid gamma-globulin, all await illumination. From the immunological point of view the investigation of multiple sclerotic patients for antibodies to neural tissue or for abnormal immunological responses to known viruses has hardly begun, while the examination of unaffected relatives for evidence of constitutional abnormalities in the mechanisms of hypersensitivity and immunity offers a completely unexplored field. Finally, from the therapeutic aspect a definite answer is awaited on whether the clinical course of multiple sclerosis is in any way influenced by the administration of substances known either to inhibit antigen-antibody reactions or to suppress their inflammatory manifestations. The fundamentalist view that such investigations must await elucidation of the intimate neurochemistry of the myelin sheath shows a curious misreading of the lessons of medical history.

We are entirely responsible for the views expressed, but wish to thank Dr. E. J. Field and Dr. Douglas McAlpine for their helpful criticisms and suggestions.

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The International Labour Office has produced two large volumes entitled *International Directory of Institutions Engaged in Study, Research, and Other Activities in the Field of Occupational Safety and Health*. These volumes list organizations in 40 countries concerned with research and other activities in the field of occupational safety and health. Further information about obtaining copies of this compilation may be obtained from the Chief of the Occupational Safety and Health Division, International Labour Office, Geneva.

C

STEROID METABOLISM IN A CASE OF CONGENITAL ADRENAL HYPERPLASIA

BY

C. L. COPE, D.M., F.R.C.P.

Postgraduate Medical School of London, W.12

During recent years the metabolic disorder in congenital adrenal hyperplasia that leads to pseudohermaphroditism in females has been a subject of great interest. This was stimulated by the dramatic demonstration by Wilkins *et al.* (1950) that administration of cortisone led to a remarkable relief of the symptoms and apparently restored the disordered metabolism to normal. Many diseases of uncertain aetiology are relieved by cortisone even when adrenal steroid metabolism appears to be normal, so that no conclusions could be drawn from the relief of symptoms alone. But it was soon shown that two manifestations of the disordered steroid metabolism—the excessively high 17-ketosteroid excretion in the urine and the excretion of the unusual steroid pregnantriol in the urine—are both promptly brought under control with return to normal values after cortisone administration. These points indicated clearly a gross disorder of adrenal cortical metabolism which was corrected by cortisone administration.

Evidence then collected that production of hydrocortisone by the adrenal cortex was seriously impaired in this disorder. Thus both Ely *et al.* (1953) and Bongiovanni *et al.* (1954) showed that the blood levels of circulating hydrocortisone were abnormally low in this disease, and soon afterwards Eberlein and Bongiovanni (1955a) found that the metabolites of hydrocortisone in the urine were also present in abnormally small amount.

To explain this syndrome of high 17-ketosteroid excretion, excessive pregnantriol excretion, and defective hydrocortisone production, Jailer (1953) postulated an enzymatic block of congenital origin in these subjects whereby they were unable to convert 17-hydroxyprogesterone, the probable normal precursor, to hydrocortisone itself. This would normally involve the action of a 21-hydroxylase, and this enzyme he suggested was lacking in congenital adrenal hyperplasia. This suggestion of Jailer's went far to explain the metabolic anomaly in the disease, and has found wide acceptance.

But hints began to appear that the condition was not as homogeneous and the explanation not always so simple as Jailer's hypothesis would suggest. It had been recognized since 1951 (Shepard and Clausen, 1951; Wilkins *et al.*, 1951) that a variant of the clinical disorder exists in which hypertension is a major feature. In 1955 Bongiovanni and Eberlein investigated one such patient and found strong evidence that the derangement of steroid metabolism was different in this patient from that previously encountered. There was, for instance, a relatively small pregnantriol excretion, but an excessively large excretion of a steroid, commonly called tetrahydro S, which differs from the usual metabolites of cortisone and hydrocortisone in having no hydroxyl group on the 11 carbon atom. In the urine of this patient no metabolites were found which contained the 11-hydroxyl grouping, and it appeared, therefore, that the defect in this variant of the disorder was not of the more usual 21-hydroxylase, but of a different enzyme, 11-hydroxylase. A unified concept of the derangement in congenital adrenal hyperplasia was thus no longer tenable. Other

facts have also emerged which are difficult to fit in with the original conception of a single enzyme deficit.

Since the paper by Butler *et al.* (1939) it has been recognized that another clinical variant of congenital adrenal hyperplasia exists in which a strong Addisonian or salt-losing tendency is a major clinical feature. It was natural to assume in such patients that, in addition to a congenital inability to form hydrocortisone, there was also a similar inability to form aldosterone, but both Luetscher and Curtis (1955) and Prader *et al.* (1955) have found normal or even high excretions of aldosterone in such subjects. Now aldosterone contains in the molecule both a 21-hydroxyl and an 11-hydroxyl grouping, so that both these enzymes must have been functioning during the synthesis of this steroid.

Still further difficulties of accepting without qualification the original hypothesis have been raised by more recent observations of Bongiovanni and Eberlein (1958). They have found that in 5 out of 12 cases investigated considerable quantities of tetrahydrocortisone were present in the urine. Now, tetrahydrocortisone is one of the first products of metabolic degradation of hydrocortisone in the body. It probably does not arise from other sources, and its presence in the urine is generally regarded as evidence of production of hydrocortisone. Bongiovanni and Eberlein (1958) have attempted to explain their most recent finding. They point out that the quantities of tetrahydrocortisone found, though within the normal range, are in fact small compared with the intense adrenal activity and the large amounts of pregnantriol excreted. They suggest that the intensity of adrenal activity is increased until small amounts of hydrocortisone are formed despite the difficulties. To quote their own words: "In some patients, by virtue of tremendous adrenocortical overactivity, the adrenals manage to secrete enough hydrocortisone to maintain normal electrolyte balance."

Observations made on a patient seen at this hospital render such an explanation difficult to accept and suggest that still further variants of the original metabolic disorder are likely to be encountered.

Case Report

The patient, aged 22, presented the typical history, clinical features, and abnormalities of the classical female congenital adrenal hyperplasia with its pseudohermaphrodite picture. She was presented as such at the Endocrine Section, Royal Society of Medicine (Ibbertson and Fraser, 1958). An enlarged clitoris was noted at birth. Childhood was in other respects normal, but growth is thought to have ceased at the age of 11 years. Excessive hair growth began on the body at 7 to 8 years. There was primary amenorrhoea, and a tendency to baldness began at the age of 18. At the time of investigation she was short, muscular, hirsute, and had no breast development. A common urogenital sinus and a small uterus were present. Radiography after air injection suggested bilateral adrenal enlargement. Urine 17-ketosteroids were 280 mg. daily, 17-ketogenic steroids 160 to 200 mg. daily, and pregnantriol excretion 31 and 96 mg. on two successive occasions. The response to therapy with 9α-fluorohydrocortisone was prompt and typical, urinary steroid excretion falling by the fourth day of treatment to 17-ketosteroids 10 mg., 17-ketogenic steroids 7 mg., and pregnantriol 0.7 mg. daily. An estimate of plasma hydrocortisone by Dr. D. Abelson, using internal isotope check (Bondy and Upton, 1957), gave only 1.7 μg. per 100 ml., a figure about one-tenth of the mean normal.

Our interest in the atypical aspects of this case was aroused by the discovery of large quantities of tetrahydrocortisone in the urine.

Analysis of the urinary steroids by the method of Cope and Hurlock (1954) indicated an excretion of 3.9 mg. of tetrahydrocortisone and 0.53 mg. of tetrahydrocortisol. With this method the normal range has been 1 to 3 mg. daily for tetrahydrocortisone and 0.2 to 1.2 mg. of tetrahydrocortisol. Thus the amount of the latter steroid excreted daily was within the normal range, but that of the former was in excess of the quantity usually encountered. Traces of free steroid were also found in the urine which had some properties suggestive of hydrocortisone and cortisone, but the amounts of these were at the lower limits of detection—around 20 μg. a day—and they were not adequately identified.

A test designed to measure the daily hydrocortisone production rate using ^{14}C-labelled hydrocortisone, and based on the assumption that all the excreted tetrahydrocortisone is derived from degradation of hydrocortisone (Cope and Black, 1958), gave an estimate of daily hydrocortisone production between 24 and 32 mg. The hydrocortisone production thus appeared to be above the maximum normally encountered in non-pregnant women. This surprising result based on analysis of the excreted tetrahydrocortisone made it necessary to obtain further evidence of the true nature of the steroid found in the urine, which appeared to be tetrahydrocortisone. A variety of tests were therefore made to establish this steroid's true nature, and these are summarized in the accompanying Table.

Tests for Identity of Tetrahydrocortisone (T.H.E.)

	Authentic T.H.E.	Steroid in Patient
Ultra-violet absorption at 240 mμ	Nil	Nil
Blue tetrazolium reaction	+++	+++
Flow rate as % of cortisol:		
(1) Toluene/prop. glycol.	42	44
(2) $CHCl_3$/formamide	100	100
(3) Benzene/formamide	84	85
Acetate R_F in E4 system* % of reference dye	280	285

* E4 solvent system of Eberlein and Bongiovanni (1955b).

In all four chromatographic systems tested the patient's steroid moved at the same rate as authentic tetrahydrocortisone or its diacetate and remained a homogeneous spot. Only small traces of a reducing steroid were present in the zone expected for tetrahydro-S, but when 50 mg. of Reichstein's compound S (pregn-4-ene-17α:21-diol-3:20-dione) was given by mouth, 1.9 mg. of tetrahydro-S was found in the subsequent 24-hour urine after glucuronidase hydrolysis, the quantity of tetrahydrocortisone and of tetrahydrocortisol remaining unchanged in this urine. This was a normal response.

When 75 mg. of cortisone acetate was given in three divided doses over 24 hours to the patient at a time when she was under metabolic control with maintenance cortisone therapy, the excretions of tetrahydrocortisol and tetrahydrocortisone showed the expected (normal) increase to a total of 4.8 mg. in the subsequent 24 hours. Readily detectable quantities of both cortisone and hydrocortisone appeared in the urine, the amounts of these being estimated at 95 and 63 μg. a day respectively. These also are normal amounts to appear after cortisone ingestion.

Discussion

Under normal conditions there is little doubt that all, or practically all, of the tetrahydrocortisone found in the urine is derived from the breakdown of hydrocortisone. If this is also true in the patient under consideration then a daily production of between 24 and 32 mg. of hydrocortisone must have taken place. This figure may be compared with the normal output for young women, which is between 6.5 and 23 mg., with a mean of about 11 mg. daily. The output observed in the patient before treatment thus lies above the extreme upper limit of the normal range; it is similar to that seen in the last month of pregnancy, being two to two and a half times as much as the mean normal expected in a non-pregnant woman (Cope and Black, 1959).

Now, Bongiovanni and Eberlein (1958), endeavouring to explain the presence of hydrocortisone in the urine of their patients, imply an attempt on the part of the abnormal adrenal to produce by its hyperactivity sufficient hydrocortisone for minimal needs. While a compensatory hyperactivity is clearly possible, such a large apparent hydrocortisone production is scarcely to be explained in this way. It is most improbable that any such compensation process would lead to excessive hydrocortisone production, since the stimulus to over-activity is presumably thereby destroyed.

But the adrenal cortical steroid metabolism is known to be abnormal in this patient, and it cannot be assumed, therefore, that all the tetrahydrocortisone found in the urine was certainly derived from endogenous hydrocortisone, although this is probably true in the normal adrenal cortex. Thus it cannot be concluded with certainty that an actual production of 24 mg. or more of hydrocortisone took place. Indeed, this seems improbable in view of the very low plasma hydrocortisone level. The test with ^{14}C-labelled hydrocortisone in this patient led to the recovery of a normal proportion of the radioactivity in the urinary tetrahydrocortisone. It can therefore be accepted that the metabolic pathway for the degradation of any hydrocortisone formed was essentially normal. But the metabolite may have been derived from some other source.

If it is assumed that the tetrahydrocortisone found in the urine has been derived, in part at least, from some other source than hydrocortisone degradation, although no such process is at present recognized, certain conclusions can nevertheless be drawn. The amount of tetrahydrocortisone and tetrahydrocortisol excreted in the urine daily was 4.4 mg. These steroids, like hydrocortisone, possess hydroxyl groups attached to both 17 and 21 carbon atoms. The 17-hydroxylase and the 21-hydroxylase enzymes must therefore have both been present in this patient, and must have been active enough to provide for the synthesis of at least 4.4 mg. of hydrocortisone if other links in the chain of hydrocortisone formation were in working order. Such a quantity represents about 70% of the minimum daily secretion rate found in normal young women (Cope and Black, 1959). Tetrahydrocortisone also contains an oxygen atom at the 11 carbon atom, and sufficient of the appropriate enzyme, 11-hydroxylase, must also have been present to provide at least 4.4 mg. of hydrocortisone daily. Furthermore, any failure of 11-hydroxylation relative to the other enzymes might have been expected to lead to excessive quantities of the steroid tetrahydro-S in the urine. Only traces of this were detected, but when compound S was fed by mouth plentiful amounts of the corresponding tetrahydro-S appeared in the urine, showing both that the mechanisms for excretion and conjugation of this metabolite were in working order, and also that our own techniques for its detection were effective.

Thus there is evidence that all three of the enzymes, deficiency of any one of which might lead to the congenital adrenal hyperplasia syndrome, are in this patient endowed with some activity, almost sufficient, indeed, to furnish minimal hydrocortisone needs.

Though the amount of tetrahydrocortisone in the urine was large, the quantity of tetrahydrocortisol was less proportionally. Such an excess of the former metabolite over the latter may be caused by administering cortisone acetate. It was just possible, therefore, that cortisone was being produced in the body, but that this relatively inert steroid was not being converted into hydrocortisone because of lack of the appropriate enzyme, an 11-β hydrogenase. This possibility was effectively excluded by the fact that when cortisone acetate was administered orally both cortisone and hydrocortisone appeared in the urine in approximately equal amounts, the usual result in normal or even in adrenalectomized persons (Cope and Hurlock, 1954).

Thus in this patient it was the reduced activity of the essential enzymes rather than their complete absence that seems to have been the fundamental deficiency of steroid metabolism. It would therefore seem that the metabolic defect encountered in congenital adrenal hyperplasia is not an all-or-none phenomenon, but may vary considerably in degree as well as in type. If this is so then milder degrees of the metabolic defect are likely to be encountered, especially perhaps in the at present rather ill-defined group of hirsute young women.

Summary

Investigations into the derangement of steroid metabolism in a case of congenital adrenal hyperplasia are described and discussed.

Generous quantities of tetrahydrocortisone, the major metabolite of hydrocortisone metabolism, were excreted by this patient.

The disorder was associated with only partial deficiency of the 21-hydroxylase, 11-hydroxylase, and 17-hydroxylase enzymes.

It is suggested that the disorder is not of the all-or-none type, but that varying degrees, as well as different types, of the metabolic defect are likely to be encountered.

Thanks are due to Professor Russell Fraser for allowing the study of his patient, and to Miss Sylvia Hughes for technical assistance.

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New Zealand has agreed to take, and be fully responsible for, 20 handicapped refugee families, 55 people in all, as part of a United Nations effort to clear refugee camps in Europe. Hitherto it has not been possible for families with handicapped members to emigrate as a unit, since handicapped refugees were admitted to overseas countries only in exceptional cases and where private sponsors were available. New Zealand's decision follows discussions last year with Dr. A. R. LINDT, the U.N. High Commissioner for refugees.

LATE PROGNOSIS OF CHLORPROMAZINE JAUNDICE

BY

A. G. MELROSE, M.D., F.R.F.P.S., M.R.C.P.Ed.

AND

J. R. ROY, M.B., F.R.F.P.S., M.R.C.P.Ed., D.P.M.

From the Southern General Hospital, Glasgow

Jaundice, the best known of the complications of chlorpromazine therapy, has an incidence of about 1%. The prevalence in a general hospital population has been investigated by Graham (1957), who noted that, of 55 patients admitted in one year suffering from jaundice, chlorpromazine was the cause in five cases. The clinical, pathological, and biochemical features have been extensively investigated—for example, by Werther and Korelitz (1957)—and are now well recognized. It is believed that jaundice is caused by hypersensitivity to the drug within the liver, which may result in an increased permeability of the cholangioles (*British Medical Journal*, 1957). The characteristic histological picture is one of biliary stasis, with infiltration of the portal tracts by polymorphs, among which eosinophils are frequent; portal-zone fibrosis and hepatic cellular damage are either slight or absent.

In most patients the period of jaundice is brief, lasting a few weeks only; but in 10% of a group of cases collected by Brick and Buckley (1957) jaundice persisted for three months or longer. Unless there is serious coexisting disease, clinical recovery is eventually complete. Little is known, however, of the ultimate effect, if any, of chlorpromazine jaundice on liver structure and function. The aim of the present investigation has been to ascertain whether disappearance of the jaundice is followed by complete histological and functional restoration.

Two patients were studied after clinical recovery from chlorpromazine jaundice. Neither had suffered previously from liver disorder, and no clinical stigmata of chronic liver disease were noted while they were under observation. The purpose of the investigation was explained to the first patient and her consent was obtained. In the case of the second subject, who was a certified patient, permission to investigate was obtained from his nearest relative and from his regular medical attendant. The results of tests which showed no abnormality have been omitted.

Case 1

A woman aged 52 was admitted to hospital on January 30, 1957, for treatment of a depressive illness with agitation. Chlorpromazine in dosage of 200 mg. daily was given from February 5 to March 5. Clinical jaundice, with typical changes in liver-function tests, was first noted on February 28 and had disappeared by April 8. She was discharged on May 14. Thereafter she was observed as an out-patient, apart from two subsequent occasions when for brief periods she was admitted to hospital for the purpose of liver biopsy. The relevant biochemical data are recorded in the Table.

Result of Liver-function Tests in Case 1

Date	Serum Bilirubin (mg./100 ml.)	Alkaline Phosphatase (K.A. Units)	Bromsulphthalein Retention (%)
6/2/57	0·2	4·9	
19/2/57	0·3	7·6	
5/3/57	6·0	53·8	
9/3/57	8·0	43·8	
11/3/57	4·0	46·4	
19/3/57	1·0	38·8	
26/3/57	0·5	38·7	
2/4/57	0·6	30·3	
5/4/57	0·6	—	26·3
9/4/57	0·2	31·9	
19/9/57	0·2	13·3	4·8
24/3/58	0·2	10·3	3·0

Needle biopsy of the liver on March 13, while jaundice was present, showed cellular infiltration of the portal tracts with a moderate fibrous-tissue reaction; the liver cells were normal (Fig. 1). The examination was repeated on September 21, and revealed little change (Fig. 2). A third liver biopsy on March 25, 1958, showed considerable fibrosis in the portal zones with slight cellular infiltration. No bile-duct proliferation was observed and the liver cells remained normal in appearance (Fig. 3).

Case 2

A man aged 48 had been a certified patient in a mental hospital for 14 years. At first his illness had been characterized by depression, with delusions, outbursts of temper, and ideas of influence and of reference. Suicide had been attempted. More recently he had been morose, suspicious, and hallucinated. Electric convulsion therapy had conferred little benefit. Treatment with chlorpromazine in dosage of 225 mg. daily was begun on October 11, 1956. Jaundice appeared on October 30 and persisted until February 1, 1957. A second course of chlorpromazine, 300 mg. daily, was followed by recurrence of jaundice on

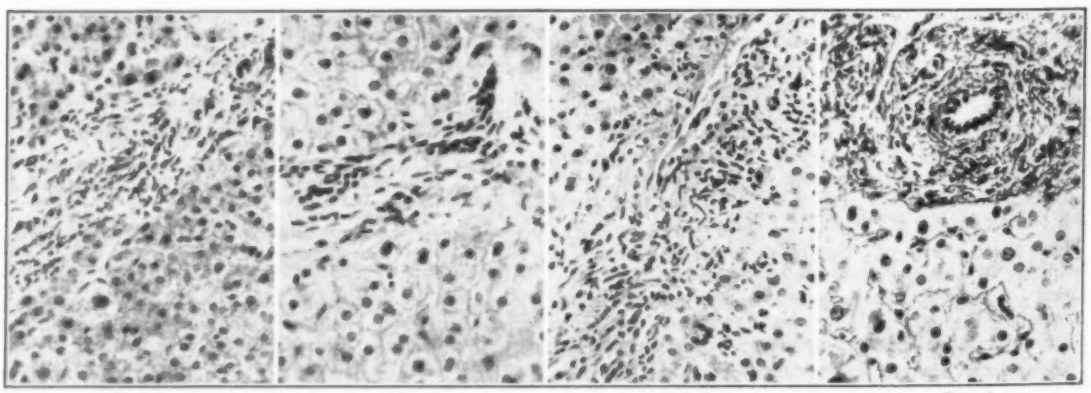

FIG. 1 FIG. 2 FIG. 3 FIG. 4

FIG. 1.—Case 1. Cellular infiltration in portal zone with moderate fibrous-tissue reaction. Normal bile duct and parenchymal cells. (H. and E. ×240.) FIG. 2.—Case 1. Some persistent fibrosis in portal tract. (H. and E. ×294.) FIG. 3.—Case 1. Portal zone shows considerable fibrosis with slight cellular infiltration. Liver cells normal. No bile-duct proliferation. (H. and E. ×240.) FIG. 4.—Case 2. Considerable amount of newly formed fibrous tissue around portal tracts. Minimal cellular infiltration. Liver cells normal. No dilatation of bile ducts or canaliculi. (van Gieson ×240.)

September 27, 1957. The jaundice had cleared by October 29, and since that date no physical illness has been reported.

The patient was investigated in May, 1958, when the following tests of liver function were recorded: serum bilirubin, 0.4 mg. per 100 ml; serum alkaline phosphatase, 46.7 K.A. units; bromsulphthalein retention, 13.8%. Needle biopsy of the liver on March 9, 1958, showed a considerable increase in fibrous tissue in the portal tracts, with slight cellular infiltration. Bile-duct proliferation and abnormality of parenchymal cells were not observed (Fig. 4).

Discussion

Chlorpromazine is of such recent introduction that enough time has not yet elapsed for the ultimate prognosis in all patients who develop jaundice to become clear. The present investigation indicates that restoration of normal liver histology or function, or both, may be long delayed. If permanent changes were to ensue, the original, cholangiolytic, type of lesion is of a nature that could lead to biliary cirrhosis. Myres *et al.* (1957) have observed such a case; one year after the onset of chlorpromazine jaundice, biliary cirrhosis, confirmed by liver biopsy, was present and portal hypertension was also noted. Twenty patients who had apparently recovered from chlorpromazine jaundice were studied by Kelsey *et al.* (1955), and early cirrhotic changes were reported in two cases. Eleven of the 20 cases, however, had previously suffered from diseases which could have involved the liver, and, as other drugs had been used in the two cases mentioned, the authors could not be certain that chlorpromazine was solely responsible.

Sensitization reactions to chlorpromazine within the liver are believed by Shay and Siplet (1957) to occur in 25% of patients who receive the drug, and are ascribed by them (Shay and Siplet, 1958) to the presence of the chlorine atom at the carbon-2 position in the promazine molecule. Such reactions are characterized by a cellular reaction within the portal tracts.

Needle biopsy of the liver was carried out by Sims *et al.* (1955) in 18 patients prior to chlorpromazine treatment and again at its conclusion. No patient became jaundiced, and biochemical tests of liver function remained normal. Four patients developed the characteristic hepatic lesions. A similar investigation was performed by Bartholomew *et al.* (1958) on 25 patients, two of whom became jaundiced. Of 16 patients in whom the pre-treatment liver biopsies had been normal, five developed the typical histological changes. The incidence of liver reactions to the drug is therefore much higher than the frequency of clinical jaundice would indicate.

When a history of previous chlorpromazine administration is not obtained from the jaundiced patient, extrahepatic biliary obstruction may be thought responsible and laparotomy performed. Surgical intervention for diagnostic purposes constitutes an additional hazard to the patient, and had been found necessary in 17.5% of a series of cases collected by Brick and Buckley (1957). Chlorpromazine jaundice is of intrahepatic cholestatic type, and in this variety Popper and Schaffner (1957) think that surgical procedures are apt to result in parenchymatous liver injury.

Chlorpromazine is a drug which is potentially toxic to the liver, as well as to leucopoietic and other tissues. When it occurs jaundice can be prolonged, and histological changes take place in the liver in a proportion of patients who do not develop jaundice. Sensitive tests of liver function may remain abnormal for long periods after jaundice. Restoration of normal liver architecture may be long delayed, and permanent liver damage, though probably rare, has been reported. Despite its excellent general utility, these considerations suggest that chlorpromazine should be given to patients only when absolutely essential and if a less toxic drug of similar pharmacological action is not available.

Summary

Two patients who had chlorpromazine jaundice six months and one year previously have been studied by means of liver-function tests and needle biopsy. In both cases there were persistent histological changes, but biliary cirrhosis was not observed; in one case liver-function tests remained abnormal. The ultimate prognosis of chlorpromazine jaundice is discussed, and it is suggested that, since the drug is potentially toxic, it should not be used without careful consideration.

We thank Professor T. Ferguson Rodger and Dr. L. D. W. Scott for advice and encouragement in the preparation of this paper. We are indebted to Dr. A. Dick for guidance on liver histology, and to Dr. W. A. Cramond for permission to examine Case 2.

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ECTOPIC GESTATION

A STUDY OF A DECADE OF ABERDEEN CASES

BY

D. V. I. FAIRWEATHER, M.B., M.R.C.O.G.

First Assistant, Department of Midwifery and Gynaecology, University of Durham

Lately Registrar, Aberdeen Maternity Hospital and Aberdeen General Hospitals

Ectopic gestation remains a condition which exercises the diagnostic ability of the surgeon to the full, and occasional deaths still occur.

The object of this study has been to investigate the symptomatology, aetiological or predisposing factors, and prognosis of the condition. It is based on an analysis of the case records of all patients admitted within the decade 1946 to 1955 to the surgical and gynaecological wards of all the hospitals in the city of Aberdeen, and in whom the diagnosis of ectopic gestation was confirmed. (All the extrauterine pregnancies were situated in the tube, with one exception where it occurred in the ovary.)

The Investigation

There were 224 ectopic pregnancies in 215 patients, since the condition recurred in nine. Fifty-two cases were treated in the surgical wards and the remaining 172 in the gynaecological wards. Of the 215 patients, 127 resided within the city boundary, and they have been used to study the epidemiology of the condition.

A general analysis of the whole series was first made, with the following results.

Age Variation.—The youngest patient in the series was aged 17 and the oldest 43 years.

Parity.—As can be seen from Table I, 65% of the women were multiparous. This agrees with the findings

TABLE I.—*Distribution of 224 Cases by Parity*

First pregnancy	65	(29%)
Second ,,	54	(24%)
Third ,,	51	(23%) (65%)
Fourth ,,	22	
Fifth or later pregnancy	19	(18%)
No detail	13	(6%)

of Crawford and Hutchinson (1954), who state that two-thirds of all ectopic gestations occur in women who have already been pregnant at least once.

Symptomatology.—The most consistent symptom was pain (99%), whilst bleeding occurred in 71%. Pain was slightly more common than bleeding as the first symptom. The incidence of shock was higher in the cases treated in the surgical than in the gynaecological wards (27% compared with 9%), and blood transfusion was also given more frequently (55% compared with 24%)—a finding that is due to the fact that severe cases are more often sent to the surgical wards. The cases occurred with equal frequency in the left and the right tube.

Recurrence Rate.—Of the 215 patients 16 had had a previous ectopic gestation (nine during the 10 years under review and seven before 1946), a recurrence rate of 7.4%. Published figures for the recurrence rates vary from 3.5% (Miller, 1940) to 9% (Henderson and Bean, 1950).

Mortality.—The death rate was 2.2% (5 out of 224 cases). It was 1.6% for city residents only. In a comprehensive review, Crawford and Hutchinson (1954) found death rates varying from 0 to 2.9%. Table II

TABLE II.—*Five Maternal Deaths in Aberdeen*

No.	Year	Ward	Age	No. of Pregnancy	Cause of Death
1	1946	Surgical	22	1	Transfusion reaction. Uraemia
2	1947	,,	31	4	Paralytic ileus
3	1951	,,	31	Not known	Infection. Deep-vein thrombosis. Pyaemia
4	1953	Mixed	34	,,	Undiagnosed—ruptured
5	1955	Surgical	30	1	Air embolism following blood transfusion

Mortality rates:—2·2% of all cases; 1·6% of city residents only.

indicates the circumstances of each death. Two deaths were directly related to blood transfusion (Nos. 1 and 5). In two others (Nos. 3 and 4), delay in making a diagnosis was an important factor. In Case 4 death occurred from intra-abdominal haemorrhage without operation; in No. 3 pyosalpinx was diagnosed and conservative treatment given for 26 days, death occurring soon after laparotomy.

Epidemiological Study of City Resident Cases

Incidence.—In calculating the incidence of ectopic gestation, the 122 cases occurring in married women resident within the boundaries of the city of Aberdeen were related to the total legitimate births occurring in the same period. In the decade under consideration there were 31,821 legitimate births in city patients; the incidence of ectopic pregnancy was therefore 1 in 260, or 3.8 per thousand births. Peel (1955) quotes an incidence of 1 in 300 (3.3 per thousand births), and Johnson (1952) 1 in 126 (8 per thousand). (In the latter series 50% of the population was negro, amongst whom ectopic pregnancy is known to be more common.) The extremes quoted vary from 3.3 (Schumann, 1921) to 9.5 per thousand (Beacham *et al.*, 1948). Even allowing for differences due to errors in sampling technique, it would appear that the incidence is definitely related to the type of population under survey. The high incidence in negro populations may be related to a high incidence of salpingitis.

Age/Parity Distribution.—The incidence in primigravidae and multiparae by age is shown in Table III. The incidence increases steadily with age, especially in primigravidae.

TABLE III.—*Aberdeen Married City Patients. Incidence by Age*

Age:	-24		25-29		30-34		35-39		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
Primigravidae	16	0·25	12	0·38	7	0·60	4	0·78	39	0·35
Multiparae	10	0·23	25	0·36	22	0·40	17	0·44	74	0·36

No detail of parity in 9 cases.

Subsequent History of Primigravidae with Ectopic Pregnancy

An attempt was made to interview personally the 39 city primigravidae who had had ectopic pregnancies in the decade under review, but only 24 could be traced.

At interview, details of further pregnancies were noted, and where none had occurred an attempt was made to find out whether the sterility was voluntary or involuntary. The patients seemed very willing to talk freely and discuss their problems. In only one case had any attempt been made to postpone further pregnancy, and this was because of social and domestic circumstances. All wanted further pregnancy, and those who had failed to conceive again were rather overanxious. In some cases of failure frigidity appeared to be developing, and in two cases there were definite indications that the home and married life were breaking up.

Of the 24 interviewed, 12 (50%) had achieved one or more additional pregnancies; in two cases it was a second ectopic gestation. Both women were in the age group 30–34 at the time of the first ectopic pregnancy.

Table IV shows that the prognosis for further pregnancies becomes poor over the age of 30. In the 30–34 age group, two out of the three further

TABLE IV.—*Analysis of Interviews by Age at Time of First (Ectopic) Pregnancy*

Age:	-24	25-29	30-34	35+	Total
Interviewed	8	7	5	4	24
Further pregnancy	5	4	3	0	12

pregnancies were recurrent ectopics; the third patient, who had a normal pregnancy, was delivered by caesarean section (as a precautionary measure).

The low fertility subsequent to the ectopic pregnancy might be due to late marriage, and the results were therefore analysed by the patient's age at the time of marriage. Of the 24 patients, 21 married before the age of 30. The incidence of subsequent pregnancy was the same in those married before 25 and in the 25–29 age group—about one-half. None of the three women who were over 30 at the time of marriage had a further pregnancy. The patient's age at the time of marriage does not appear to be important in the prognosis for further pregnancy in this series.

Finally, the interval between marriage and the first (ectopic) pregnancy was investigated to find whether

relative infertility was a factor. It is apparent from Table V that of the 12 patients who had no further pregnancy adequate explanation was found in 5: one had proved tuberculosis of the tube; one had bilateral salpingectomy performed at the time of operation; one had hydrosalpinx of the remaining tube; in one salpingitis was found at subsequent laparotomy; and one had been trying for only six months for further pregnancy. Of the remaining seven where no lesion could be demonstrated, one was in the 25–29 age group, two were in the 30–34 age group, one was in the 35–39 age group, and three were in the 40–44 age group. Six of the seven were thus over 30, and three of the seven had been married for over six years before the first pregnancy was achieved.

TABLE V.—*Analysis of Interviews by Years Married Before (Ectopic) First Pregnancy (Figures in Parentheses Indicate Age at Time of First Ectopic Pregnancy)*

Years	Interviewed	Further Pregnancies	No Further Pregnancy
<1	3	2 had 2 (20-24) 1 ,, 3 (20-24)	—
1–2	3	1 ,, 2 (20-24) 1 ,, 1+1 abortion (25-29)	1 (25-29)
2–3	8	2 had 1 (25-29)	1 tuberculous salpingitis 1 bilat. salpingectomy 1 hydrosalpinx } (20-24) 1 (30-34) 2 (40-44)
3–4	2	1 had 2 (20-24) 1 ,, ectopic after 2 years (30-34)	—
4–6	3	1 had 1 after 3 years (30-34) 1 had ectopic after 3 years (30-34)	1 salpingitis (25-29)
6+	5	1 had 1 after 18 months (25-29)	1 (25-29) (trying only 6 months) 1 (30-34) 1 (35-39) 1 (40-44)

It appeared, therefore, that in younger women who failed to have a further pregnancy there was evidence of a pathological lesion of the tube in almost every case. The majority of the younger women, however, had a successful pregnancy following the ectopic pregnancy, the reason for the original ectopic pregnancy being apparently a temporary defect of some kind in the reproductive mechanism.

The women who failed to conceive again despite the absence of any obvious lesion in the pelvis were mostly over 30 years of age, and as a result had probably become rather infertile.

Discussion

Aetiology.—About two-thirds of patients with ectopic pregnancy have had one or more previous intrauterine pregnancies. In some cases resultant sepsis, more particularly salpingitis, may have been an important predisposing factor, although there is not always a clear clinical history of this. The most novel finding in the present investigation has been that the incidence of ectopic pregnancy increases steadily with the age of the mother, particularly in primigravidae. Seventy-five per cent. of the primigravidae had been married for more than two years before the ectopic pregnancy occurred, suggesting some degree of infertility. It is not easy to explain how age operates. It may lead to a general lowering of the functional efficiency of the sex hormones, uterus, and tube, or to a defect in the ovum itself. On the other hand, physical changes such as uterine or tubal fibrosis or minor degrees of endometriosis may be present. In the younger women, definite pathological conditions, especially of the tube, are often the cause. This is in line with the fact that, in populations with a low standard of living and a high incidence of gonococcal and tuberculous salpingitis, tubal pregnancy is relatively common in young women.

Conclusion

As can be seen from the analysis presented, the younger the patient the better the prognosis.

Bender (1956) found that another pregnancy occurred in 44% of cases of tubal pregnancy (made up as follows: another ectopic pregnancy, 7%; a live child, 32%; an abortion, 5%). The conception rate was 54% in women under 30 and 34% in those over 30. The outcome of the subsequent pregnancy was unaffected by whether or not the patient had had an intrauterine pregnancy prior to the ectopic pregnancy. These findings are confirmed in the present study.

I thank Professor Dugald Baird for his advice and criticism in the preparation of this paper.

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COMBINED LOCAL AND GENERAL ANALGESIA FOR CATARACT OPERATIONS

BY

JOHN IVES, M.B., B.S., F.F.A.R.C.S.

Senior Anaesthetist to the Croydon Group of Hospitals

"He now put his head betwixt his forelegs, and raising it slowly again he fell over on his side. His eye immediately became fixed. . . ."

Charles Waterton made these observations in 1812, describing his first experiment on a "medium-sized dog" with "wourali poison" (Aldington, 1949). It was not until 1947 that ocular akinesia by curare was used in eye surgery. Five years later Kirby (1952), who introduced the method, reviewed his experience with it in nearly 600 cases. His conclusions were that the relaxation during cataract surgery produced by curare, after sedation, analgesia, and local anaesthesia, is superior to, and has not been produced by, that induced by any other agent and that it is one of the pleasing features of the akinesia of curare that the surgeon can work efficiently and expeditiously and in a most delicate manner when he and the patient are relaxed.

Kirby's work stimulated others, many of whom were enthusiastic. Cordes and Mullen (1951), after using curare in 85 cases, finally came to the conclusion that curare should be used in every case of cataract extraction, for once the patient has squeezed and extruded vitreous it is too late for any relaxation-producing measures.

Barraquer Moner (1953), of Barcelona, summarizing his experience of 1,500 cases, said that the direct results of the excellent akinesia and hypotension produced by

curare are: (1) simplification of all operative manipulations, and (2) decrease in the number of accidents. Other writers reported disquieting drawbacks with the method, mostly arising from respiratory difficulties.

Bamford (1955) abandoned the use of curare after 88 cases, having had a patient who became rapidly cyanosed and unconscious. Flagg (1952), the anaesthesiologist working with Kirby, recommended that every ophthalmic surgeon using curare should be familiar with laryngeal exposure and intubation. There is therefore some justification, in spite of the manifold local advantages of curare akinesia, for Stallard (1958) writing that the practice of administering curare to a conscious patient with local anaesthesia of the eye has been abandoned in Britain.

General anaesthesia with a relaxant and intubation has been strongly advocated for cataract operations, notably by Cridland (1955), Sandiford (1955, 1957), and Condon (1956). However, most ophthalmic surgeons find it difficult to dissociate general anaesthesia from the possibility of coughing, straining, and vomiting. Despite recent advances, no anaesthetist can guarantee that these hazards will not arise. Perhaps extubation is the most critical moment: Sandiford recommends it should be done "smartly," whereas Condon states that "the tube is slowly removed. In this way the likelihood of a cough on extubation is diminished."

To avoid possible difficulties with general anaesthesia and yet eliminate apprehension and tenseness, Burn *et al.* (1955) have used the "lytic cocktail" of chlorpromazine, promethazine, and pethidine, combined with local analgesia but without any relaxant; Healy (1955) substitutes dimenhydrinate ("dramamine") for promethazine and adds tubocurarine. Good results have been reported, but again there are disadvantages. Burn (1955) writes that the pain threshold is undoubtedly raised, but it can be exceeded and the patients react sometimes in a less controlled manner than under phenobarbitone sedation. There may be a considerable fall of blood pressure, with a gradual return to pre-operative levels in six to eight hours. Emergence from this sedation usually takes up to 10 hours. On the table there is marked pallor of the face and bloodlessness of the lips, which may be alarming unless it is expected, and the skin is noticeably cold to the touch.

Gibson Moore (1955), using chlorpromazine only for sedation during four pre-operative days, has also remarked on the pallor that accompanies the full effect of this drug.

Croydon Eye Unit Technique

If the pharyngeal and laryngeal reflexes are likely to become impaired, general anaesthesia must be used. But such conditions are not a necessity in cataract surgery; what is required is an analgesic patient, in control of his own protective reflexes and yet with complete ocular akinesia and hypotonia.

A method has been developed which meets these needs and avoids the disadvantages of the techniques previously outlined. Comparatively small doses of sedative and curarizing drugs are used and general analgesia is induced with nitrous oxide before local analgesics are injected. Neither a facepiece nor an artificial airway is employed; the gas is delivered by means of a simple appliance which has been designed for the purpose. It consists of a stiffly flexible rubber-lined tube which is clamped at shoulder level to the side of the theatre table and then connected to the Boyle's machine. Near the upper end of this metal tube a small instrument tray has been attached. This serves three purposes: it supports the sterile towel as a tent above the nose and mouth, it locates the delivery tube and makes displacement less likely, and, finally, it has sufficient stability to carry the instruments used in ocular surgery.

During operation the patient lies quietly, half asleep and without restlessness or any respiratory embarrassment. His eye is invariably soft, and after removal of the lens the iris falls back on a concave vitreous surface. When the principal corneo-scleral suture has been tied the nitrous oxide is stopped and the patient is sensible and talking before leaving the theatre.

Details of Method

The night before operation the patient is given 25 mg. of chlorpromazine and an appropriate dose of amylobarbitone sodium or quinalbarbitone sodium. One and a half hours before operation he has an intramuscular injection of 25 mg. of chlorpromazine, 500 to 750 mg. of methylpentynol ("oblivon") by mouth and cocaine drops at five-minute intervals to his cornea. He comes to the theatre conscious and usually calm and co-operative. It is explained to him that he will be given a relaxing injection in the back of his hand and that a tube will be placed in front of his nose to help his breathing when under the towels.

On the table, his head is placed in the hollowed part of a rectangular sponge-rubber pillow. The nozzle of the delivery tube is adjusted so that it is 1 in. (2.5 cm.) above the chin and directed at the nasal septum (see Fig.). Neither the tube nor the towels touch the lower

Photograph showing position of appliance.

half of the patient's face. Nitrous oxide at 6 litres a minute is turned on. Pethidine, from a 5-ml. syringe containing 50 mg. diluted to 5 ml., is injected with a No. 20 needle into a vein on the dorsum of his left hand or forearm (15 to 25 mg. being the usual initial dose), and the syringe is left strapped in position. After an interval of three minutes the local injections are given by the surgeon. These consist of (1) 1.5 ml. of lignocaine 2%, with adrenaline 1 in 80,000 and hyaluronidase, placed within the cone of the recti muscles, and (2) a further 1 ml. at the outer orbital margin. The patient will look up on command, but the analgesia already developed is such that wincing is seldom seen.

When these injections are completed, gallamine triethiodide ("flaxedil") (40 mg., diluted to 5 ml. in a 10-ml. syringe) is slowly injected through the needle used for the pethidine, the initial dose being 8–16 mg. The facial expression is watched; it becomes relaxed and "ironed out"; often mask-like. This may not happen until an extra millilitre or two of the diluted gallamine has been added, but the dose of 40 mg. is not often needed and is never exceeded.

When placing the sterile towels, it is possible to cover the complete face, leaving only the one eye exposed. Two litres a minute of oxygen is now added to the nitrous oxide and the corneal incision made. Should the regular respiration quicken, a further 10 mg. of pethidine is added; this may be repeated, but never more than a total of 50 mg. is used. Occasionally the patient will snore; a hand under the towels and a finger supporting the chin quickly corrects this.

Lowered Intraocular Tension

The muscle relaxant, the pre-operative chlorpromazine, and the retrobulbar lignocaine all combine to produce a very soft eye. Most ophthalmic surgeons now agree that this is essential for a safe intracapsular extraction, and even when an extracapsular extraction is performed low tension is of advantage provided the surgeon is prepared to alter his technique to allow for it.

The great majority of the cases in this series were intracapsular extractions, the earlier ones using Arruga capsule forceps, while those undertaken in 1958 were with the mechanical erisophake. Recently, enzymatic zonulolysis with alpha-chymotrypsin by the method of Barraquer Moner (1958) has been used. In this procedure the decreased tension is felt to be essential.

When the towels are removed, the patient not infrequently says he has been dreaming and is surprised to learn that his operation has been completed. On returning to the ward he sleeps quietly. Nausea, vomiting, or restlessness is rarely reported.

Results

Since July, 1956, this method has been used for 155 cataract extractions. The ages of the patients ranged from 21 to 89, 83% being over 65. Many were hypertensive, diabetic, emphysematous, or bronchitic; two had congestive heart failure and one was hemiplegic. Two did not understand English or any common language.

In the immediate post-operative period there was an occasional complaint of feeling faint; three were restless and had to be given a sedative; only one vomited in the 24 hours following operation.

Ophthalmic complications did develop in a proportion of the cases, but it was not considered that general analgesia was responsible for any one of these.

Discussion

Gallamine Triethiodide.—Sufficient proof has accumulated to show that tubocurarine is a valuable aid in intraocular surgery, but the risk of respiratory impairment has restricted its wide acceptance in this field. Mushin *et al.* (1949), working with conscious volunteers, found that gallamine triethiodide had a similar action to tubocurarine in first affecting the eye muscles; they also found that in doses of 40–70 mg. there was no demonstrable decrease in pulmonary ventilation and that it had a shorter period of action than tubocurarine. In the present series, the total time for each operation rarely exceeded 15 minutes. It was for these reasons that gallamine was chosen. With the small doses employed we have not found troublesome tachycardia, increased salivation, or the congested eyes reported by others.

Intravenous Pethidine.—This might have been expected to increase the liability of post-operative vomiting. We attribute the low incidence in our series to the chlorpromazine given with premedication.

Nitrous Oxide Analgesia.—Various devices have been described (Marshall, 1936; Kulvin, 1956), even when local analgesia alone was used, to prevent obstruction of the airway by the sterile towels; with the introduction of curare an additional supply of oxygen was widely recommended. The appliance described is useful for both these purposes. When the method was first employed nitrous oxide was used very cautiously, the aim being to keep the patient in Guedel's first stage but believing that the second stage of delirium might easily be entered. As experience increased it was found to be surprisingly easy to keep patients in this analgesic and half-asleep plane, with regular respirations and bright pink colour; none have developed excitement or uncontrolled movements. A similar finding has been recently described in dental anaesthesia, and Klock (1955) in a paper entitled "New Concepts in Nitrous Oxide Anaesthesia" has given the name "amnalgesia" to "a very precise and well-defined plane of general anaesthesia in the first stage. It exists between what is recognized as the analgesic plane and the excitement stage." He states that it is "surprisingly wide and easily controlled."

Summary

A technique designed to produce relaxation and general analgesia or "amnalgesia" in cataract operations, without heavy sedation, intubation, or respiratory embarrassment, is described.

It has been used in 155 cataract extractions and has given conditions, for both patient and surgeon, comparable to those obtained with general anaesthesia. No complications attributable to the method have arisen.

I thank Mr. Dermot Pierse for his co-operation and encouragement, Messrs. A. Charles King Ltd. for making the appliance, and Edmée Wood for the photograph.

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EXPERIENCE WITH A GLUCOSE-OXIDASE METHOD FOR ESTIMATING GLUCOSE IN BLOOD AND C.S.F.

BY

J. E. MIDDLETON, B.M., M.R.C.P.

Lecturer in Clinical Pathology, St. Thomas's Hospital and Medical School, London

According to Joslin *et al.* (1952) the ideal blood-sugar method should meet the following requirements: (1) it should determine only glucose; (2) it should be adaptable for both macro- and semimicro-techniques; (3) the reagents should include chemicals which are relatively inexpensive and not over-hazardous to technicians; (4) the method should require a minimum of time, technique, and apparatus; (5) it should be accurate and yield reproducible results. Old-established blood-sugar methods, such as those of MacLean, Folin–Wu, Hagedorn–Jensen, and Shaffer–Hartman, are not ideal methods by the above requirements because they are elaborate and not specific for glucose. The error due to non-glucose reducing substances, the so-called saccharoids, in the blood has largely been eliminated in the procedures of Nelson (1944) and of Asatoor and King (1954); but while they yield results approximating to the blood true glucose, these methods are still relatively laborious.

Glucose oxidase, an enzyme which is highly specific for glucose and does not react with the blood saccharoids, has recently been employed for the estimation of blood glucose by Froesch and Renold (1956), Teller (1956), Huggett and Nixon (1957a, 1957b), Middleton and Griffiths (1957), Schön and Bucke (1958), and Saifer and Gerstenfeld (1958); of these methods those of Teller, and of Middleton and Griffiths, satisfy all the criteria specified by Joslin *et al.* (1952). Should such specific glucose methods come into common use, as seems desirable, a revision of the accepted normal standards would be required, since the results obtained with them represent true glucose and are therefore generally lower than those given by the usual blood-sugar methods.

The object of this article is to describe the experience obtained with one of the glucose-oxidase methods in the estimation of glucose in blood and C.S.F., with particular reference to its use in glucose-tolerance tests.

Material and Methods

The majority of the blood samples examined were obtained during the course of glucose-tolerance tests, using an oral dose of 50 g. of glucose in 100 ml. of water, from patients of both sexes and all ages. A number of samples of C.S.F. were also tested. The glucose was estimated by the glucose-oxidase method of Middleton and Griffiths (1957), using a Hilger Biochem absorptiometer and a Chance O R 2 filter. This method is satisfactory for blood-glucose values down to 30 mg. per 100 ml., but with lower values the colour produced is faint. Under such circumstances more accurate results are obtained by using a larger volume of blood filtrate—for example, 0.4 or 0.5 ml. added to 3.8 or 3.7 ml. respectively of the buffered enzyme-dye solution, and readings made against a standard containing 3 mg. of glucose per 100 ml. (corresponding to a blood concentration of 30 mg. per 100 ml.). In some instances the sugar was also determined in parallel by MacLean's method.

Capillary blood was used in the main, but venous blood was also used where estimations by more than one method were made. Thymol cannot be employed as a preservative for venous blood, since it interferes with the development of full colour in the glucose-oxidase method.

Glycosuria during the glucose-tolerance tests was detected with "clinistix."

The Blood Saccharoids

The blood-sugar and blood-glucose levels were determined on 100 specimens of blood from 37 patients; 63 were venous and 37 capillary samples, 39 of the former and 23 of the latter being from diabetic patients, the others from patients with normal glucose tolerance. The difference between the values given by the two methods, which represents the blood saccharoids, varied from 0 to 81 mg. per 100 ml. (mean 35 mg. per 100 ml.). The mean levels of these substances in the diabetic and normal venous blood samples were 30 and 27 mg. per 100 ml., a difference which is not significant, whereas the mean levels in the diabetic and normal capillary blood samples were 51 and 37 mg. per 100 ml. respectively, a significant difference ($P<0.01$). There was no correlation between the blood-saccharoid level and the blood-glucose level, which varied from 38 to 504 mg. per 100 ml., nor with the time following the ingestion of glucose during glucose-tolerance tests. The typical results in Table I show that the concentration of saccharoids fluctuates greatly during the test, and is irregular and unpredictable.

TABLE I.—*Blood-saccharoid Values in mg. per 100 ml. in the Fasting State and at Intervals After 50 g. of Glucose in 17 Patients*

Type	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours
Diabetic (venous blood)	—	34	13	81	8
	39	46	69	44	7
	22	27	24	37	40
	34	6	52	28	0
Normal (venous blood)	34	33	41	22	—
	38	10	52	17	2
	16	30	0	18	40
	34	12	35	19	47
	46	30	39	40	1
Diabetic (capillary blood)	—	29	76	76	75
	72	55	75	38	60
	—	57	75	71	41
	31	38	8	46	25
	66	62	29	25	52
Normal (capillary blood)	0	67	13	42	45
	—	43	47	24	4
	43	61	52	40	38

Glucose-tolerance Tests

The results of 106 glucose-tolerance tests in which the capillary blood glucose was estimated by the enzyme method are summarized in Table II.

TABLE II.—*Mean Capillary Blood Glucose in mg. per 100 ml. and Limits (in Parentheses) in the Fasting State and at Intervals After 50 g. of Glucose in 106 Patients*

Type of Curve	No.	Fasting	½ Hour	1 Hour	1½ Hours	2 Hours
Normal ..	36	69 (46–94)	119 (71–162)	122 (53–161)	97 (40–153)	74 (31–103)
Lag ..	16	74 (48–90)	166 (132–232)	170 (102–238)	112 (40–150)	62 (15–92)
Renal glycosuria	8	57 (24–71)	107 (75–132)	96 (54–142)	77 (20–116)	63 (18–112)
Malabsorption	3	52 (14–78)	66 (26–92)	67 (38–84)	70 (36–98)	72 (36–111)
Diabetic ..	43	118 (40–378)	198 (88–560)	247 (117–582)	252 (120–532)	220 (106–470)

Normal

The fasting capillary blood glucose in 36 patients with normal glucose tolerance varied from 46 to 94 mg. per 100 ml. (mean 69 mg., S.D. ± 13). In 29 of these the blood glucose returned to a normal fasting level two hours or less after the ingestion of glucose, no glycosuria being detected. The maximum rise recorded in these curves was to 162 mg. per 100 ml., the fasting and two-hour values in this patient being 62 and 52 mg. respectively. The two-hour blood glucose in these 29 patients was between 40 and 93 mg. (mean 70 mg.).

In the remaining seven patients tolerance was also normal except for two-hour values slightly outside these limits. One of them showed reactive hypoglycaemia, the blood glucose at two hours being 31 mg. per 100 ml. The other six had slightly high two-hour values, but in one the level of 96 mg. followed a previous fall to 66 mg. at one and a half hours. The same rebound also occurred in three other patients with normal tolerance where the terminal blood glucose did not exceed 90 mg. In four patients the blood glucose at two hours had only fallen to between 97 and 103 mg. per 100 ml.; one had fallen to 68 mg. at two and a half hours. The maximum rise recorded in these curves was to 138 mg. In the last patient, a treated acromegalic, the blood glucose in the fasting state and at half-hour intervals after glucose was 76, 150, 158, 144, and 99 mg. per 100 ml. respectively; this curve was regarded as an example of the upper limit of normal tolerance. These curves are discussed later.

Lag Curves, Renal Glycosuria, Malabsorption, and Other Flat Curves

The 16 lag curves showed a rapid high rise in blood glucose above the normal renal threshold, glycosuria being detected, and a return of the blood glucose to a normal fasting level in two hours. The lowest maximum rise recorded in these curves was to 168 mg. per 100 ml. These patients had alimentary glycosuria with otherwise normal tolerance, and, considered with the normal curves, showed that as a clinical guide the normal renal threshold for glucose may be regarded as being in the region of 160 mg. Reactive hypoglycaemia occurred in one patient, the two-hour blood glucose being 15 mg. The two-hour levels in the other 15 varied from 36 to 92 mg. (mean 65 mg.).

Eight patients showing either a normal rise in blood glucose or flat curves, all with glycosuria, were considered to have renal glycosuria. Fasting or two-hour blood-glucose levels were below 36 mg. per 100 ml. in three patients. One patient was pregnant.

The three curves labelled malabsorption were flat, the rise in blood glucose being less than 33 mg. per 100 ml., but no glycosuria was detected. One remained below 38 mg. throughout the two hours, and a second rose steadily from 78 to 111 mg. at two hours. These patients had idiopathic steatorrhoea, tuberculous peritonitis, and regional ileitis, respectively.

Six additional curves not recorded in Table II were flat, the rise in blood glucose being less than 30 mg. per 100 ml., and no glycosuria was found. The fasting blood glucose was below 40 mg. in four patients. Two of the patients had hypopituitarism, the other four had hypoglycaemic symptoms of undetermined cause.

Diabetic Curves

The diabetic curves showed a prolonged high rise in the blood glucose, which did not return to a normal fasting level in two hours. All were associated with glycosuria excepting four where the peak blood glucose was between 174 and 216 mg. per 100 ml. A raised renal threshold for glucose was presumed to be present in these cases. The fasting blood glucose was below 90 mg. in 17 patients, between 90 and 100 mg. in a further six, and above 100 mg. in the other 20. In six patients the maximum rise recorded was to between 150 and 165 mg., the fasting blood glucose being from 58 to 96 mg., and the two-hour level in five of them between 111 and 120 mg., and 163 mg. in the sixth. These curves were thought to show slight reduction of glucose tolerance. In the other 37 curves the peak blood glucose was more than 174 mg. and the two-hour level more than 126 mg. except in four, where it was between 106 and 116 mg. per 100 ml.

In three patients with severe hepato-cellular insufficiency, curves showing slight loss of glucose tolerance but without glycosuria were obtained. These are not included in Table II.

Insulin-sensitivity Tests

Tests were performed on three patients using an intravenous dose of 0.1 unit of insulin per kg. body weight. Two cases of hypopituitarism showed increased sensitivity, the fasting blood-glucose levels of 65 and 71 mg. per 100 ml. falling to 8 mg. (at 45 minutes) and 34 mg. (at one hour) and rising again to 32 and 42 mg. at two hours respectively. The third patient had a normal response, the fasting value of 70 mg. falling to 26 mg. at 45 minutes and rising to 52 mg. at one hour. Hypoglycaemic coma did not occur in the patient whose blood glucose fell to 8 mg.

C.S.F.

Glucose was estimated by the enzyme method in 29 samples of C.S.F. and was found to vary from 50 to 76 mg. per 100 ml. (mean 63 mg., S.D. ± 7). These specimens were all from patients with diseases not associated with known changes of the C.S.F. glucose concentration, and hence the results are considered to be within the normal range. Estimations of the sugar concentration by MacLean's method were also performed in parallel on 20 of these specimens. The saccharoids varied from 7 to 42 mg. per 100 ml. (mean 19 mg.).

Discussion

In the early stages of this work the normal fasting capillary blood glucose as determined by the enzyme method was reported to be from 50 to 90 mg. per 100 ml. (Middleton and Griffiths, 1957). This was based on parallel estimations in glucose-tolerance tests, using the enzyme method and those of Asatoor and King and of MacLean, and on fasting levels found in a small number of normal persons. The further experience reported in this article has slightly extended these normal limits, which, as Table III shows, are very similar to those found by others when using glucose-oxidase methods.

Other workers have found a variable and frequently high level of saccharoids in the blood. Thus Mosenthal and Barry (1946, 1950), using the methods of Folin–Wu and Lauber and Mattice (1944), found the level to vary from 1 to 78 mg. per 100 ml. in 200 determinations on diabetic and non-diabetic venous blood, and that in 38% it exceeded 30 mg. These authors also found that the level was unpredictable and variable during glucose-tolerance tests, and that it could not be correlated with

TABLE III.—*Normal Fasting Blood Glucose as Estimated by Glucose-oxidase Methods*

Author	Specimen	No. of Subjects	Blood Glucose in mg. per 100 ml.	
			Mean	Normal Range (Mean ± 2 S.D.)
Renold (1957) ..	Venous blood	52	68	48–88
Teller (1958) ..	Serum	7*	82	67–97
Huggett (1958) ..	Venous Blood	18	77	59–95
Present series ..	Capillary blood	36	69	43–95
Schön (1958) ..	" "	41	73	49–97
Saifer and Gerstenfeld (1958)	Plasma	36	87	69–105

* The first reported blood-glucose values as determined by a colorimetric enzyme method.

age, diet, or insulin requirements. Haunz and Keranen (1950) compared the results obtained with the Folin–Wu and Nelson–Somogyi methods on venous blood, and found in 66 diabetic patients a difference of from 2 to 72 mg. per 100 ml. (mean 30.6 mg.) and in 34 normal persons from 8 to 49 mg. (mean 26 mg.). Saifer and Gerstenfeld (1958) showed the saccharoid level to be higher in diabetic than in normal blood plasma.

Further work will be necessary to determine what importance is to be attached to the difference between the saccharoid levels in normal and diabetic capillary blood reported in this article.

The reason for the erratic variations of the blood saccharoids remains obscure, and their identity is also far from clear, although Mosenthal and Barry (1946) were of the opinion that they have no significance in carbohydrate metabolism. If this be true the assessment of the ability of the body to metabolize glucose will be achieved more precisely from the behaviour of the true glucose than from the total reducing substances. Because of the additionally variable and unpredictable arteriovenous glucose difference in blood, Mosenthal and Barry (1950) considered that true glucose determinations on venous blood furnish the most dependable data on which to evaluate glucose tolerance. The interpretation of glucose-tolerance curves from capillary blood-sugar values is also held by many to be often difficult. The results of the present study show, however, that when capillary blood is used from convenience or necessity a satisfactory and accurate assessment can usually be made when the blood glucose is determined by the enzyme method. A slightly high two-hour value in an otherwise normal curve can be explained by the inevitable error of technique, by a rebound following a previous unrecorded fall to a normal fasting level, or by a slight delay in the return to this level, the latter being found in some normal persons, especially the elderly and when using capillary blood. Curves of these types were observed in this study, but their true significance is seldom in doubt when their general form is taken into consideration.

It is commonly held that virtually all the reducing substance in C.S.F. is glucose. It is now shown, however, that there is not infrequently an appreciable amount of saccharoids in this fluid, although the level is not as high as in blood, owing presumably to the absence of red cells. The normal C.S.F. glucose as determined by the enzyme method in a small number of patients was in the same range as that accepted for the normal C.S.F. true glucose.

Summary

The results obtained with a glucose-oxidase method for estimating glucose in blood and C.S.F. are recorded.

The blood sugar (MacLean's method) and blood glucose were determined in parallel on 100 samples from diabetic and non-diabetic patients. The non-glucose reducing substances (saccharoids) in these samples varied from 0 to 81 mg. per 100 ml. (mean 35 mg.), the mean level being significantly higher in diabetic than in normal capillary blood; a significant difference was not apparent in venous samples. No correlation was found with the blood-glucose level nor with the time following ingestion of glucose in glucose-tolerance tests; erratic and unpredictable changes occurred throughout the tests.

The fasting capillary blood glucose in 36 patients with normal glucose tolerance varied from 46 to 94 mg. per 100 ml. (mean 69 mg.). The normal renal threshold for glucose was found to be in the region of 160 mg. per 100 ml.

In 115 glucose-tolerance tests and 3 insulin-sensitivity tests blood-glucose estimations on capillary blood provided a satisfactory assessment of tolerance. It is considered that the determination of glucose tolerance on the basis of blood glucose has advantages over the older blood-sugar methods.

The normal C.S.F. glucose varied from 50 to 76 mg. per 100 ml. (mean 63 mg.) in 29 patients. A mean value of 19 mg. was found for the saccharoids in this fluid.

I am grateful to Dr. W. J. Griffiths, in whose department this work was performed, for contant help and encouragement: My thanks are also due to Professor A. St. G. Huggett, Dr. A. E. Renold, Dr. H. Schön, and Dr. J. D. Teller for permission to quote their hitherto unpublished results; and to Miss C. Powell, who did many of the glucose-tolerance tests.

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The Ciba Foundation was honoured during the year by a grant of armorial bearings from the Earl Marshal. The blazon reads: sanguine (the colour of life) three regular hexagons on their points (for chemistry); on a chief dovetailed or, five annulets interlaced sable (for international co-operation). The crest is a cock, sable, holding a staff of Aesculapius (for medicine). The supporters are: dexter, a wyvern, or, langued gules (for the founder) differenced by a sword of St. Paul, gules (for London); and sinister, a lion rampant, or, langued gules (for Britain), differenced by a crozier of Basle, sable (for the founder). The motto "Consocient Gentes" means "Let the nations come together."—*Report for 1958*, the Ciba Foundation.

REPORT ON THREE EXTENSIVE INDUSTRIAL CHEMICAL BURNS

BY

J. S. CASON, F.R.C.S.Ed.

Consultant Surgeon, Burns Unit, Birmingham Accident Hospital

Extensive chemical burns are fortunately rare, which speaks well for the safety precautions taken to protect personnel in industry. At the Birmingham Burns Unit, which serves a population of about four million, we have seen only three cases in the last five years.

But when chemical burns of the skin occur they are often disfiguring and disabling, and sometimes fatal. The risk to life depends on the amount of skin destruction, the degree of absorption, and the toxicity of the chemical to the kidneys and liver. The three cases reported here illustrate some of the clinical problems involved in diagnosis and management.

Case 1. Cresylic Acid Burn

Whilst at work a man aged 47 fell into a vat of "ardrox" (a cresylic acid derivative). His clothes were removed quickly and he was washed thoroughly under a shower before being transferred to hospital, where an intravenous infusion of 5% dextrose in saline was started. Six hours later he was transferred to the burns unit, where he was found to have burns amounting to 15% of the body surface (excluding erythema), involving the buttocks, genitalia, lower limbs, and forearms. The burns consisted of brown staining of the skin without blistering. All the areas were hypersensitive to pin-prick and the burns were apparently superficial partial skin loss. There were certainly at that time no areas of full-thickness skin destruction.

Three hours after admission he began to vomit, and oral fluids were stopped, these being replaced by 4.3% dextrose in 0.18% saline intravenously.

Thirty-six hours after the injury it became apparent that anuria had developed, and conservative measures comprising use of glucose, arachis oil, and a restricted fluid intake were started (Bull *et al.*, 1949). This mixture was not tolerated, and 50% intravenous dextrose was substituted through a "polythene" catheter into the superior vena cava. Calcium gluconate, glucose, and insulin were used to control the serum potassium (Meroney, 1956), and, in view of the anuria, only a single dose of oxytetracycline 500 mg. was given to combat infection (Wilkinson, 1955). However, the blood urea rose steadily to 528 mg./100 ml. and the serum potassium to 9.3 mEq/l., and the patient died on the tenth day.

The patient's condition, apart from renal insufficiency, had appeared satisfactory until the seventh day, when he developed generalized rhonchi in both lungs, a pericardial rub, and precordial pain. The precordial pain disappeared on the ninth day. On the tenth day he became unconscious and developed congestive heart failure, dying within 18 hours of becoming comatose. During these last hours his heart failure was treated with intravenous digoxin and the acidosis with intravenous 1/6-molar sodium lactate. Electrocardiograms showed changes consistent with hyperkalaemia (Fig. 1), and, although a dramatic change towards normality occurred after he was given digoxin (Fig. 2), a fatal outcome was not prevented. Unfortunately, permission for a necropsy was not granted.

Case 2. Chromic Acid Burn

A man aged 47 slipped at work and plunged his arm into a vat of chromic acid. He received an extensive burn of the whole of the right upper limb. The burn was immediately washed with water, and 45 minutes after the accident he was admitted to the burns unit, where the arm was again generously washed in "buffer solution." This is a mixture of monobasic and dibasic phosphate which has the following composition: monobasic potassium phosphate (KH_2PO_4), 70 g., and dibasic sodium phosphate ($Na_2HPO_4.12H_2O$), 180 g., in 850 ml. of water; this makes 1,000 ml. of solution (Bull and Jackson, 1952).

The area of the burn was 9% of the body surface. The skin of the arm and forearm was stained yellow, and the appearance and texture were consistent with a diagnosis of full-thickness destruction. The skin was also analgesic to pin-prick. In contrast, some skin on the hand and in the axilla was sensitive to pin-prick, and skin loss appeared to be partial only.

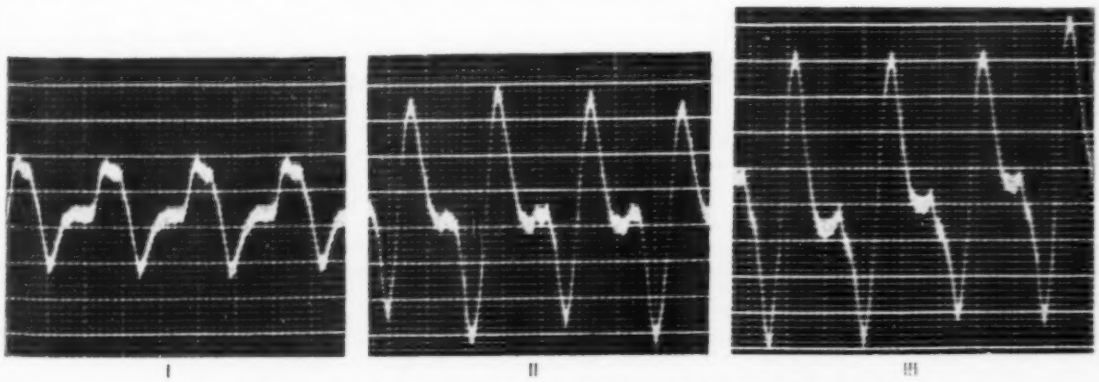

FIG. 1.—Case 1. E.C.G. leads I, II, and III when the serum potassium was 7.5 mEq/l.

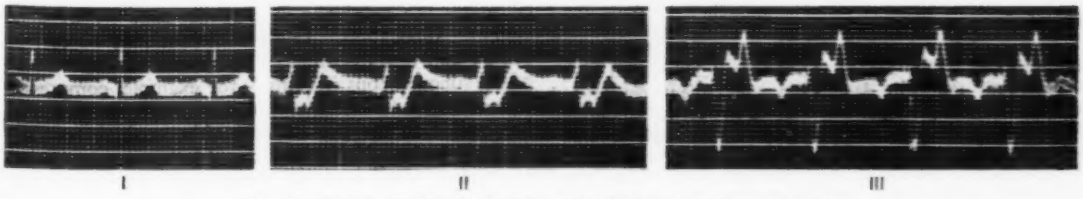

FIG. 2.—Case 1. E.C.G. leads I, II, and III after intravenous digoxin.

Seventy-five minutes after the accident, and as quickly as could be arranged, the patient was anaesthetized and the dead skin of the arm and forearm excised. The skin and most of the subcutaneous fat were removed, leaving only the larger veins and some areolar tissue. In spite of this deep excision, many small thrombosed veins were clearly seen in the deep fascia at the first few dressings after operation—that is, the acid had already penetrated deeply into the fat before excision. The partial skin burn on the hand and in the axilla, amounting to a loss of 2%, was not excised.

It was not possible to graft the resulting raw area until about three weeks later owing to a surface layer of necrotic fatty tissue and small thrombosed veins, but after three weeks' treatment with penicillin cream (1,000 units/g.) the "clean" granulating area was successfully grafted in one operation. The patient, who was discharged from hospital 44 days after injury, developed no renal or liver damage (cf. Pascale *et al.*, 1952; Samitz, 1955), and no other toxic effects could be found.

Seventeen hours after injury his urine had a specific gravity of 1028, with a trace of protein. There was no sugar in it; the benzidine test for blood was negative, and there were no absorption bands on spectroscopy. Microscopy showed an occasional hyaline cast and red cell only.

Microscopical examination of the excised skin showed the epidermis to be absent and there was coagulative necrosis of most of the dermis, particularly the upper half or two-thirds involving dermal epithelium. In the deeper third of the dermis the dilated congested capillary network suggested capillary stasis. Here coagulation of the sweat coils had not occurred, but some showed evidence of early disintegrative necrosis.

Blood and urine examination four months after injury showed no evidence of renal or liver damage.

Case 3. Nickel Sulphate and Acid Burn

A man aged 62 slipped and fell into a vat of hot acid nickel-plating solution; he managed to climb out quickly, and first-aid at the factory consisted in application of sodium bicarbonate. The hot solution was a mixture of nickel chloride (8 oz. to a gallon; 50 g. to a litre), nickel sulphate (50 oz. to a gallon; 320 g. to a litre), boric acid (6 oz. to a gallon; 38 g. to a litre), and cumarin (5 lb./100 gallon; 500 g./100 l.). It was at a temperature of 178° F. (81° C.) and had a *p*H of 3.5. He was admitted to hospital 40 minutes after the accident and the burns were treated again with a "buffer solution" compress. The burn covered 40% of the body surface and had the appearance of only partial destruction of the skin.

Shock was treated by plasma transfusion, using serial haematocrits, and blood-volume estimations, using radio-active isotopes (^{32}P and ^{51}Cr). His breathing on admission was rapid, deep, and sighing, and in view of the acidity of the solution into which he had fallen 450 ml. of 1/6 molar lactate solution was given intravenously, followed by plasma. The respiratory rate slowed with this treatment. The CO_2 combining power on admission was later reported as having been 22 mEq/l.

Nickel was detected in the urine and serum, and, in view of the possibility of toxic complications, dimercaprol was given (Gilman and Goodman, 1956).

Owing to vomiting within three hours of admission fluids could not be taken orally, and the fluid requirement had to be given intravenously through a polythene catheter into the inferior vena cava.

Urine output and osmolarity readings showed that the solute cleared by the kidney varied from 1,270 to 630 mEq a day until the fifth day, when the patient developed hypotension and pre-renal oliguria. Daily serum and urine electrolyte and urea measurements were taken, and deficiencies of sodium and potassium treated accordingly. Hyponatraemia occurring on the fifth and final day responded dramatically to intravenous 5% saline, an unconscious and apparently moribund patient being rendered conscious and rational for a few hours at a time. Noradrenaline was tried as treatment for the hypotension of the fifth day. Though the blood pressure responded to a continuous graded intravenous administration, the urine output and general condition did not improve. He finally succumbed to pneumonia. Penicillin and tetracycline were used to combat infection. No nickel was found in the urine after the third day.

At necropsy, lobar pneumonia and oedema of the lung were the only significant findings apart from the burned area of skin, most of which, in contrast to its initial appearance, turned out to be mostly full-thickness skin loss.

Discussion

From the point of view of extent and depth, extensive chemical burns presumably carry the same risk to life as thermal injuries: sometimes, also, the burning agent is both hot and caustic and the burn is mixed. In either event the patient may die from shock, ischaemic renal failure, infection, or exhaustion. Provided the toxic chemical is not absorbed sufficiently to damage vital processes the burn is a surface lesion only, and as soon as it is neutralized therapeutically or by tissue protein it ceases to differ appreciably from a similar thermal injury.

The peculiar risks of some extensive chemical burns, however, depend upon the absorption and toxicity of the chemical, which may damage the kidneys or liver enough to be fatal apart from the local skin lesion.

Measures to prevent absorption of the chemical or to remove it fall into four groups—namely, washing from the surface, neutralization, removal of the tissue reservoir, and facilitation of detoxication or excretion.

Immediate Removal of Clothing and Washing

These are the most effective first-aid measures, done under a shower if necessary, and good washing facilities should always be available when men work in proximity to toxic chemicals. The immediate removal of contaminated clothing cannot be unduly stressed, as fatal absorption of chemical may occur very rapidly. A case has been described where a man did not remove his clothing contaminated with nitrobenzene: he died within an hour, and his blood was "like chocolate" owing to methaemoglobinaemia (Hamilton, 1919). Men who have neglected to remove clothing contaminated with methyl alcohol have been blinded (Hunter, 1957).

Heat is evolved when concentrated sulphuric acid is mixed with water and may produce a thermal burn of the skin; in such a case the acid should be washed off first with anhydrous ethyl alcohol (Hunter, 1957). Washing off is made easier sometimes by adding another chemical, as in the case of trinitrophenylmethylnitramine (tetryl): the hands should be washed in running water with the addition of 5% sodium sulphite to convert it into a water-soluble substance (Silver, 1938).

Neutralization of the Chemical

In different circumstances this can be applied on, into, or under the skin, and it may be done by local or systemic application. Local treatment may be carried out by applying the antidote on the surface of the skin or by subcutaneous injection—for example, compresses of monobasic and dibasic phosphate buffer solution may be applied to the skin surface after washing for acid or alkali burns. Hydrofluoric acid burns may be treated by surface application of magnesium oxide paste and subcutaneous injection of 10% calcium gluconate,

magnesium, and calcium fluoride, being relatively harmless and insoluble (Jones, 1939). Again, oxidation by means of local application of sodium hypochlorite is one of the ways of neutralizing aromatic arsines.

An example of systemic administration of an antidote is the use of atropine for organic phosphorus insecticides. Here atropine is used parenterally because these insecticides are powerful cholinesterase inhibitors.

Surgical Removal of Toxic Chemical in Tissues

This means excision of skin and fat in the case of chemical burns, to remove the reservoir of chemical within the body (Case 2).

The management of a burn with a toxic chemical is simplified if the case is suitable for surgical excision. Washing, neutralization, and excision can then all be completed with the greatest speed. If the burn is on the limbs there is probably a place for the immediate application of a tourniquet until after the burn is excised, but this should be done under medical supervision. Copious fluids, unless and until there is evidence of oliguria due to renal damage, are easy to provide, orally or intravenously. Where the site of the burn excludes the use of a tourniquet, the operation blood loss, and consequent transfusion, may even result in some benefit from part exchange of the blood volume.

Surgical excision is eminently suitable for full-thickness burns, but a difficult problem is presented by burns of doubtful depth. Should they be excised or not? On the one hand, excision may be the patient's only chance of survival; on the other hand, it costs him an operation, a large permanent scar, a longer healing-time—and all these may be unnecessary if the dose of chemical which could be absorbed is sublethal. The difficulty is not a technical one: it is not very hard to excise a large area of skin and subcutaneous tissue provided enough blood is available (Topley and Jackson, 1957). The problem turns on our inability to know if there is a lethal dose of chemical in the burned skin, and if it will be, or has already been, absorbed.

In some cases—for example, poisoning by the aromatic nitro- and amino-derivatives—spectrophotometric estimation of the concentration of methaemoglobin will indicate the severity of the poisoning. Heinz bodies, punctate basophilia, and polychromatophilia are valuable early signs of poisoning by dinitrobenzene and aniline. Coproporphyrinuria is an early sign in trinitrotoluene poisoning, and may be fifty times greater than normal in a fatal case (Hunter, 1957). Even in these cases, where it is possible to investigate poisoning with simple tests, the surgeon still never knows whether there is a further risk from the chemical remaining in the skin.

To be at all confident of making the right decision in these circumstances, the surgeon needs to know whether previous similar patients with burns of that size, caused by that strength of that particular chemical, lived or died. These cases are rare, and reports of them are virtually non-existent in medical literature.

The diagnosis of the depth of burning is always difficult, and this difficulty is increased in burns with some chemicals such as phenol (Jackson, 1953). But sensitivity to pin-prick always indicates partial-thickness skin loss at the time of examination, although this may later become whole skin loss owing to the action of the chemical (Case 3). Analgesia to pin-prick does not necessarily imply full-thickness loss.

Facilitation of Detoxication or Excretion of Toxic Chemical

If a large dose of the chemical is absorbed in spite of these measures, survival will depend largely upon increasing its excretion in a copious dilute urine. Possibly, exchange transfusions or the artificial kidney may be useful for this purpose, but we have no experience of this form of treatment.

Dimercaprol has been found extremely useful in treating intoxication by arsenical, mercurial, cadmium, and heavy metals drugs. It destroys the complexes formed between the metal and body proteins and increases the rate of excretion of the metal in its detoxified form (Gilman and Goodman, 1955). In Case 3 the dimercaprol probably protected the enzyme systems against any ill effect of nickel (Gilman and Goodman, 1955) and also produced a beneficial diuresis ("acetazolamide effect"), incidentally increasing sodium excretion at a time when a burned patient would be expected to have sodium retention.

Summary and Conclusions

Three cases of extensive chemical burns are presented.

The various methods of treating these burns are surveyed.

The problems involved in the diagnosis of chemical burns requiring surgical excision are discussed.

Publication of short histories of such cases, treated successfully and unsuccessfully, with details of the solution, burn, timing, treatment, and outcome, would be the first step towards more rational management. Meanwhile one must bear in mind the potentially serious nature of these injuries and be correspondingly bold and thorough in efforts to save life.

I thank Dr. J. P. Bull, Director of the Medical Research Council Industrial Injuries and Burns Research Unit, and Mr. D. MacG. Jackson, surgeon in charge of the burns unit, for their helpful criticism and advice.

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"Many sick people need no more than medical care to enable them to return to their old way of life. But many live among difficulties whose complications cannot be escaped easily, and for them effective help in illness may require the efforts of several professions working together. The almoner's particular sphere of knowledge is largely that common to caseworkers, of human responses in the face of difficulty and pressure, and of ways of supporting a man's individuality and integrity against odds. She must in addition have special understanding of the personal effects of illness and of the associations between social problems and illness; and she must appreciate the place and the responsibilities of social work in the medical world and its relationship with social service outside."—*Annual Report of the Institute of Almoners, 1957–58.*

TENSILE STRENGTH OF IRRADIATED FREEZE-DRIED ARTERIAL GRAFTS

BY

T. HORNE, M.A., B.Sc., A.R.I.C.

A. V. POLLOCK, M.B., B.Sc., F.R.C.S.

AND

K. S. ZINNEMANN, M.D.

From the Departments of Surgery and Bacteriology, University of Leeds, and the Wantage Radiation Laboratory

For several years in Leeds arterial homografts have been preserved by sterilization in β-propiolactone followed by freeze-drying and storage *in vacuo* (Flewett *et al.*, 1955; Zinnemann, 1957). Bacteriological and histological tests on these arteries after reconstitution have shown satisfactory sterilization and preservation of structure. Tensiometer tests have revealed a significant gain in tensile strength (unpublished observations).

Recently we have been interested in the application of γ-radiation from a cobalt or caesium source to the sterilization of arterial homografts. This paper deals with the effects of such irradiation on the tensile strength of freeze-dried human aortas.

Methods

Aortas from young cadavers were obtained without sterile precautions. Two equal lengths were taken from each aorta and freeze-dried separately by the single-stage method (Flewett *et al.*, 1955). One length from each aorta was sent to the Wantage Radiation Laboratory, where it was exposed in its tube to a dose of γ-radiation from ^{60}Co source at either 20° C. or −15° C. The other length of each aorta was retained as a control. Finally all arteries were reconstituted with physiological saline solution, and six to nine 1-cm. rings were cut from each aorta with a double-bladed guillotine. The rings were suspended between two wire hooks attached to a Denison textile tensiometer. The wires were distracted at constant speed and the breaking load of each aortic ring was recorded in pounds.

Results

Preliminary work on the tensile strength of aortic rings had shown no significant difference between the strength of the thoracic and that of the abdominal aorta. It had also shown that significant weakening occurred in aortas exposed to 2.5×10^6 rad, 2×10^6 rad, and 1.5×10^6 rad. It is certain that a smaller dose than 2×10^6 rad cannot be relied on to sterilize tissues—and this dose will not sterilize freeze-dried cultures of clostridia (A. J. H. Rains, personal communication). It was therefore decided to test the effect on tensile strength of 2×10^6 rad γ-radiation on five aortas at 20° C. and five at −15° C. The results are shown in Tables I and II. It is clear that irradiation causes weakening, more marked at 20° C. but still significant at −15° C.

Discussion

The possibility of using ionizing radiation for the destruction of micro-organisms in arterial grafts was first mooted by Meeker and Gross (1951a, 1951b). These authors irradiated five fresh dog arterial segments with 1.5×10^6 rep (equivalent to about 1.4×10^6 rad) of high-energy electrons at room temperature. When these segments were grafted into dogs they failed owing to thrombosis in each case. On the other hand, 38 aortic grafts irradiated with 1.5 to 2×10^6 rep at −80° C. were transplanted into the abdominal aortas of dogs with only one failure.

Buchanan and Marrangoni (1955) irradiated freeze-dried arterial segments with 2×10^6 rep of γ-radiation from ^{60}Co source. They found that when these grafts were reconstituted they were sterile and usable, and that there were no histological changes. They did not record the long-term results of implanting these arteries in dogs.

The destructive effects of irradiation on tissues are threefold: (1) Ionization of organic molecules with direct breakdown of tissues. (2) Ionization of water molecules with the production of free H^+, OH^-, and other ions, which cause oxidation and reduction effects. (3) The direct heating effect of electron irradiation. This effect is negligible with γ-radiation sources because they take longer than electrical machines to achieve the desired dose.

TABLE I.—*Arteries Irradiated at 20° C.*

Artery No.	Mean Tensile Strength (lb. per cm. Ring)		Mean Difference (lb.)	t	n	p
	Control	Irradiated				
1	7·17	4·17	3·00	8·89	12	<0·001
2	5·63	3·70	1·93	4·87	12	<0·001
3	5·89	3·49	2·40	4·23	16	<0·001
4	7·96	4·80	3·16	6·51	14	<0·001
5	5·19	4·30	0·89	2·53	12	<0·05 >0·02
1–5	6·38	4·07	2·31	8·53	74	<0·001

TABLE II.—*Arteries Irradiated at −15° C.*

Artery No.	Mean Tensile Strength (lb. per cm. Ring)		Mean Difference (lb.)	t	n	p
	Control	Irradiated				
1	6·84	5·84	1·00	1·55	12	<0·2 >0·1
2	7·07	4·66	2·41	4·54	12	<0·001
3	7·96	6·16	1·80	2·54	12	<0·05 >0·02
4	8·78	7·05	1·73	2·38	10	<0·05 >0·02
5	8·70	7·17	1·53	2·63	12	<0·05 >0·02
1–5	7·84	6·15	1·69	4·96	66	<0·001

It was hoped that by irradiating freeze-dried material (water content under 4%) at a reduced temperature the latter two effects could be eliminated and sterility obtained without structural damage. The reduction in tensile strength demonstrated in this series apparently reflects damage not detectable histologically. As our results with β-propiolactone sterilized freeze-dried arteries show an actual increase in tensile strength, we shall continue to prefer this method.

Summary

Ten human aortic segments have been freeze-dried and then exposed *in vacuo* to 2×10^6 rad of γ-radiation from a ^{60}Co source.

Five of these grafts were irradiated at 20° C. and five at −15° C.

The tensile strength of rings of each aorta with its control non-irradiated aorta was tested on a Denison machine.

In each case a reduction in strength was found in the irradiated compared with the control artery.

It is suggested that γ-radiation at 20° C. or at −15° C. is an unsatisfactory sterilizant for arterial homografts.

The tensile strength measurements were carried out by one of us (A. V. P.) in the Department of Textile Industries of the University of Leeds. We are greatly indebted to Professor J. B. Speakman and Mr. W. J. Onions for their help and advice.

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VULVAL VARICOSE VEINS IN PREGNANCY

BY

HAROLD DODD, Ch.M., F.R.C.S.
Surgeon, St. Mary's Hospital Group, Paddington: King George Hospital, Ilford; and London Royal Homoeopathic Hospital

AND

H. PAYLING WRIGHT, Ph.D., B.Sc., L.M.S.S.A.
Research Assistant, Obstetric Unit, University College Hospital Medical School, London

The proportion of young women who first develop or show deterioration of varicose veins of the legs during pregnancy is high. In the antenatal department of University College Hospital a weekly varicose vein clinic has been established to advise mothers concerning this condition and to attempt, by antenatal care, to reduce the incidence of puerperal phlebitis and thrombosis.

This varicose vein clinic received about 8% of all women booked for antenatal care during the period 1955–7 (343 cases of varicose veins from a total of 4,267 bookings). This figure does not represent the true incidence of the condition, for only those women who complained of pain or disfigurement, or whose condition was so severe that it attracted attention at the routine blood-pressure examination, were referred to the vein clinic. Hence the figure of 8% in this selected group is a conservative one, and the proportion of women with some degree of incompetence is probably nearer 12%, or even higher. This high incidence is especially important when it is remembered that the majority of women accepted for antenatal care are young primiparae; in multiparae, who are not usually seen in hospital, the proportion with varicose veins must be higher.

Though varicosities of the leg veins in pregnancy are widely recognized, involvement of the veins of the vulva have hitherto received little attention. During the routine examination of the women in the antenatal clinic, however, the frequency of such varicosities has impressed itself upon us. The probable reason why the condition has so far apparently been overlooked is due to the natural reticence of most of the women, who nevertheless are often extremely uncomfortable because of the bulk, tension, and warmth of one or both labia majora, especially in the posterior part.

Of the 343 women seen in the varicose vein clinic, 80 (23.3%) had involvement of the vulva. This varied from a single node on the margin of the labium major to a mass of varices causing so much swelling that walking was difficult because of chafing of the dependent labia. Analysis of these 80 cases for (1) site of varicosity, (2) week of gestation when first observed by the patient, and (3) parity of the patient are set out in the Table, together with similar figures for leg varices in the 343 patients examined. It will be seen that there is little difference in incidence between the right and left sides, and that the majority developed after the 26th week of gestation. Though the figures for parity are not a true indication of incidence, for, as stated earlier, primiparae predominate in the antenatal clinic, the figures available show clearly that multiparous women suffer more frequently from vulval varicose veins than do women having their first child.

Analysis of Varicose Veins in Pregnancy

Site		Week of Onset		Parity	
Vulval Varicosities (80 Cases)					
Right side ..	40 (33%)	12–26 weeks	46 (19·5%)	Para 0 ..	15 (11·8%)
Left ,, ..	31 (27·5%)	27 weeks–term	34 (32%)	,, 1 ..	31 (28%)
Both sides ..	9 (8·5%)			,, 2 ..	13 (28%)
				,, 2+	21 (37%)
Leg Varicosities (343 Cases)					
Right side ..	121	12–26 weeks	237	Para 0 ..	127
Left ,, ..	113	27 weeks–term	106	,, 1 ..	112
Both sides ..	109			,, 2 ..	47
				,, 3 ..	57

The percentages are based on the number of women with corresponding leg varices

Treatment of Varicose Veins in Pregnancy

The treatment of varicose veins in pregnancy resolves itself into expectant and operative measures. Most of the patients referred to one of us (H. D.) had gross distressing varices that were not responding to bandaging, elastic stockings, injections, and extra rest. In many instances the home circumstances required the mother's services until the day of delivery, whilst a few patients had veins which were unrelieved except by continuous recumbency for the last 6 to 12 weeks of pregnancy. These groups have been treated operatively.

In considering varicose veins in pregnancy, a diagnosis is first required. Most of these patients had frank incompetence of the long saphenous vein; it was often present before conception. An impulse was palpable in their veins when they coughed. Percussion of the long saphenous vein at the groin gave a discernible impulse in varices of the leg. The tourniquet tests gave down-filling waves or cascades. Fifty such patients have been treated by a flush sapheno-femoral ligation and destruction of the saphenous trunk; since December, 1951, it has been by stripping. Three patients who had incompetence of the short saphenous vein had a sapheno-popliteal ligation and stripping to the ankle.

Varicose Veins of the Vulva

Varicose veins of the vulva are an embarrassing form of varicosity which is distressing mentally and physically. Vulval veins may be distended from one or more of three sources of hypertension. (1) The long saphenous vein through its incompetent tributaries, the superficial and deep external pudic veins. (2) The spermatic veins passing with the round ligament from the labia majora into the inguinal canal and thence to the posterior abdominal wall to join the inferior vena cava on the right and the renal vein on the left. Their varicosity causes a bulge in the groin like an inguinal hernia, with an increasing pear-shaped swelling of the

labium major on the affected side, attaining grotesque proportions in the perineum. Apart from its disfigurement, the mass is an embarrassment and a discomfort during sitting and walking. (3) The pudendal tributaries of the internal iliac vein also fill varices of the perineum, posterior part of the labia, and upper part of the postero-medial aspects of the thigh. Fortunately after parturition these veins disappear; it is therefore only those of exceptional extent that require surgical treatment.

Diagnosis.—This is difficult in the vulval and perineal varices. Varicosity of the long saphenous and round ligament veins together has been found four times. The varicose round ligament veins would correspond to a varicocele of the spermatic veins in the male. They are denoted by a bulge in the inguinal canal, which steadily enlarges to the labium major and perineum. There is an impulse in these veins on coughing. Compression empties them, and they are largely controlled after emptying by pressure with the finger over the internal ring when the swelling remains smaller and softer, but reappears immediately the pressure is released. This control is not absolute, for there are usually contributory vessels from the long saphenous or pudendal veins.

Treatment.—Where clear signs of venous incompetence were found, which was causing considerable distress not relieved by other measures, operation has been advised, up to the end of the seventh month. Varicosity of the labium major requires exploration of the sapheno-femoral junction and its ligation if incompetent, together with the tributaries joining here, followed by excision of the round ligament with the associated distended veins. This is done under a bland general anaesthetic.

Operation

The patient is tilted into a 10 degrees head-down supine position which materially reduces the size of the veins and the bleeding.

The incision extends from the anterior superior iliac spine to the pubic tubercle and curves on to the thigh for 1 in. (2.5 cm.). The procedure consists of two steps.

1. *The Sapheno-femoral Junction is Defined.*—This requires division of the tributaries of the long saphenous vein, being the superficial external pudic, superficial epigastric, superficial circumflex iliac, antero-lateral, and postero-medial veins; the superficial external pudic vein may be greatly enlarged. After the ligation of these veins it is possible to open the foramen ovale and inspect the femoral vein, especially its medial aspect, for the presence of the deep external pudic vein which is present in 40% of cases and may be obviously varicose. This is ligated with thread. The sapheno-femoral union is tied and transfixed.

2. *Veins of the Round Ligament.*—The upper flap of the wound—that is, skin and subcutaneous tissue—is reflected to expose the surface of the external oblique and the external abdominal ring. The distended veins are visible as they enter the ring. The external oblique aponeurosis is split in the line of its fibres (as in a hernial operation) from the apex of the external ring to beyond the internal ring—that is, two-thirds of the way to the anterior superior iliac spine. The two leaves of the external oblique are reflected generously to expose the cremaster and conjoined tendon. A large vein from the superficial fat passes into the external ring and is divided between ligatures (haemostats tend to tear fragile varicose veins). The upper leaf of the external oblique is wiped off the internal oblique towards the rectus abdominis. The cremaster and its contained bulky mass of veins and the round ligament are wiped up off Poupart's ligament and also off the pubic tubercle until it can be elevated out of the inguinal canal on the finger. A large vein passing between it and the pubic tubercle is divided. The cremaster is separated along its fibres from the conjoined tendon above and divided just lateral to the internal ring until, with the round ligament, it is free from abdominal musculature; the cremasteric vessels are divided in the process. The round ligament and its veins are drawn taut at the internal abdominal ring and divided after transfixion with a secure ligature. The large veins immediately shrink and become manageable; they have a few connexions posteriorly, including a considerable one at the medial border of the internal ring. This is divided. The mass is gently elevated and stroked clear from the fat below the pubic tubercle and drawn out of the labium major. Several vessels need securing in the process and gradually the mass of dilated veins emerges from the labia and is removed.

Varicose Veins from the Peripheral Tributaries of the External Iliac Vein

When it is recalled that the uterine vessels enlarge to 30 to 40 times their normal size in pregnancy, it is not surprising that other tributaries of the internal iliac vein participate in this increase, especially the peripheral ones. In our experience its pudendal tributaries may become varicose. One such patient has been operated on by exposing the lower internal border of the gluteus maximus and dividing the enlarged veins running from the perineum. The procedure gave worth-while relief.

Results

No mother or baby has suffered from the procedure. All patients have agreed that their operation was beneficial, many have had one and two babies since, and one has had three. Our experience leads us to advise operation where there is real need.

Summary

Distressing vulval varicose veins occurred in 80 women from a total of 4,267 who booked as antenatal patients in a large teaching hospital—that is, about 2%.

The majority of these varicosities were first apparent after the 26th week of gestation.

The incidence rose with parity.

The diagnosis of various anatomical types of vulval varicosities is discussed.

Eradication of such vulval varicosities during pregnancy is frequently beneficial and details are given for the surgical approach for each type.

City Life in Japan, by R. P. Dore (Routledge & Kegan Paul, London, price 45s.), is published as a volume in the International Library of Sociology and Social Reconstruction. The author lived in a lower middle-class district of Tokyo for several months in 1951 and carried out a social survey there, examining standards of living, family life, community life, and religion and morality. The chapter he devotes to "Health and Security" is a useful summary of public-health methods in a Japanese municipality. Much is expected of the individual householder, whose sense of communal duty seems to be strongly developed. A public-health campaign in 1951 was supported by posters declaiming, "A flush toilet is the first condition of civilized living," and as a result of this some 90% of houses in the district were connected to the main sewer. There is a high degree of health consciousness among the people, and families spend quite large amounts of money on medicines and doctors' fees. Most sophisticated middle-class households possess their own hypodermic syringe and ampoules for injections. The author remarks that "the increase in the number of abortions reported yearly since the operation became legal in 1948 has been of astonishing proportions."

SUBACUTE COMBINED DEGENERATION DEVELOPING DURING LIVER THERAPY

BY

J. F. ADAMS, V.R.D., M.B., F.R.F.P.S.
M.R.C.P.Ed., D.Obst.R.C.O.G.
Western Infirmary, Glasgow

AND

G. C. TIMBURY, M.B., F.R.F.P.S.
Royal Mental Hospital, Glasgow

"Initial treatment of the disease is easy, it is over maintenance treatment that the patient comes to grief." Witts made this statement in 1934, when liver and liver extracts were the only forms of therapy available for the treatment of pernicious anaemia.

Parenteral liver therapy is still in common use, and we report here the unfortunate consequences of the use of two such preparations, which were later found to contain only trivial quantities of vitamin B_{12}.

Case 1

A man aged 66 was seen by us 16 years after his pernicious anaemia had been diagnosed. During this period he had received the same brand of liver extract, 2 ml. intramuscularly every fortnight. For the two years prior to our examination he had experienced ataxia and paraesthesiae of the legs; there was a brief history of glossitis.

He was not obviously anaemic, but had signs of subacute combined degeneration—namely, increase of patellar reflexes, absence of ankle reflexes, left extensor plantar response, calf tenderness, and absence of vibration sense in the left leg. He had a mild macrocytic anaemia; Hb, 10.3 g./100 ml., R.B.C., 3,000,000/c.mm.; P.C.V., 33%; M.C.V., 110 cubic microns; and sternal marrow biopsy showed megaloblastic erythropoiesis. Acid was not detected in the gastric juice after histamine stimulation (Kay, 1953). The serum vitamin-B_{12} level was subnormal (25 $\mu\mu$g./ml.)—method of Ross (1952) and Hutner *et al.* (1956). Absorption of ^{60}Co B_{12} was subnormal by the urinary excretion test (Schilling, 1953), but was raised to normal by the addition of intrinsic factor.

Treatment with parenteral vitamin B_{12} restored the peripheral blood levels to normal and abolished the glossitis and paraesthesiae. The objective neurological signs were unchanged after six months' intensive treatment.

A sample of the liver extract was obtained from the patient's doctor, and was found to contain 0.09 μg. of vitamin B_{12}/ml., measured by microbiological assay.

Case 2

A man aged 59 was admitted to hospital with a marked anaemia. Pernicious anaemia had been diagnosed 10 years before admission, and he had received the same brand of liver extract, 2 ml. intramuscularly each month, until a month before admission, when the injections were given weekly. He was pale and icteric, the spleen and liver were palpable, both plantar responses were extensor, and the patellar and ankle reflexes were diminished. Peripheral blood examination showed a macrocytic anaemia: Hb, 4.1 g./100 ml.; R.B.C., 1,390,000/c.mm.; and sternal marrow biopsy showed megaloblastic erythropoiesis. Acid was absent from the gastric juice. The serum vitamin-B_{12} level was subnormal (45 $\mu\mu$g./ml.). Absorption of ^{60}Co B_{12} was subnormal by the urinary excretion test.

The patient died suddenly and unexpectedly in acute left ventricular failure shortly after treatment was begun. At post-mortem examination the stomach was atrophic, the liver enlarged and fatty, red marrow extended along the length of a femur, and the lungs were oedematous; no anatomical cause for the cardiac failure was found. The liver extract with which the patient had been treated was found to contain 1.5 μg. of vitamin B_{12}/ml., measured by microbiological assay.

Discussion

Addisonian pernicious anaemia and subacute combined degeneration are manifestations of vitamin-B_{12} deficiency resulting from absence of intrinsic factor. The standard treatment is by parenteral vitamin-B_{12} therapy, but parenteral liver extracts still enjoy some popularity, their use being largely a matter of tradition. The haemopoietic effects of liver extracts are believed to be due entirely to their vitamin-B_{12} content.

The object of therapy is to raise and maintain the serum vitamin B_{12} to a normal level. The serum vitamin-B_{12} levels can be estimated only by the laborious technique of microbiological assay. Mollin and Ross (1953) showed that the individual requirement for vitamin B_{12} varies widely from case to case, and suggested that as a general rule maintenance treatment should consist of 40 μg. of vitamin B_{12} intramuscularly every 10 days or 160 μg. intramuscularly every 21 days. With these figures in mind we have reviewed the liver extracts commonly used in this country (see Table); it

Vitamin-B_{12} Content, Dosage, and Cost of Liver Extracts

Manufacturer	Preparation	Stated Vitamin B_{12} Content	Maintenance Dose Recommended by Manufacturer	Cost of Recommended Maintenance/Month
1	a	Not stated	1–2 ml. every 4–5 weeks	4d.–8d.
	b	5 μg./ml.	4 ml. ,, ,, 3–4 ,,	1s. 1d.–1s. 5d.
2	a	2 ,,	8 ,, ,, 4 ,,	6s.
	b	4 ,,	4 ,, ,, 4 ,,	6s.
	c	20 ,,	1–2 ,, ,, 4 ,,	3s. 6d.–7s.
3	a	2 ,,	5 ml. every week or 2 weeks	5s.–10s.
			1–2 ml. alt. days	7s 6d.–15s.
	b	20 ,,	1 ml. every 1–2 weeks	4s. 6d.–9s.
4	a	Not stated	2–4 ,, ,, week	4s. 8d.–9s. 4d.
	b	20 μg./ml.	1–2 ,, ,, 2–4 weeks	10d.–3s. 4d.
5	a	Not stated	2 ml. "periodically"	
	b	"High"	1–4 ml. every 4 weeks	1s. 10d.–7s. 4d.
6	a	2 μg./ml.	2–4 ,, ,, week	4s. 4d.–8s. 8d.
	b	20 ,,	2 ,, ,, 2 weeks	6s. 10d.
7	a	12 ,,	1 ,, ,, week	9s.
	b	10 ,,	4 ,, ,, 4 weeks	1s. 8d.
8	a	2 ,,	2 ,, ,, 2 ,,	2s.
9	a	10 ,,	4 ,, ,, week	6s.
	b	20 ,,	1 ,, ,, 2 weeks	5s.
10	a	2 ,,	2 ,, ,, 2 ,,	1s. 6d
11	a	Not stated	2 ,, ,, 4 ,,	1s. 4d.
Various	Vitamin B_{12}		40 μg. ,, 10 days	7d.–11d.
			160 ,, ,, 21 ,,	1s. 3d.–1s. 10d.

is obvious that with one exception (9a) the doses recommended by the manufacturer are sadly inadequate as judged by the recommendations of Mollin and Ross. It is also worthy of note that the cost of maintenance therapy with liver extracts, expensive enough when the doses recommended by the manufacturer are used, would be between 10 to nearly 80 times the cost of an equivalent amount of crystalline vitamin B_{12} if the doses of liver extract were increased to ensure that each patient received the amount of vitamin B_{12} recommended by Mollin and Ross.

Liver extracts and preparations of vitamin B_{12} may deteriorate on storage if exposed to light, but deterioration of the liver extract can hardly be regarded as playing a part in these two cases, because random samples of the preparations have been found to have a similarly low vitamin-B_{12} content. It should be mentioned that in neither case did the manufacturers state the vitamin-B_{12} content of the extract.

However much we may decry the sale of liver extracts with such vitamin-B_{12} content, it is the physician who must bear the responsibility for inadequate treatment of the patient. Until the physician is prepared to use the large dosage of liver extracts needed to ensure adequate intake of vitamin B_{12} or until the manufacturers increase the vitamin-B_{12} content of liver extracts and alter their recommendations it would seem that the only justifiable course is to use solutions of pure vitamin B_{12} in all cases.

Summary

Two patients with pernicious anaemia who relapsed and developed subacute combined degeneration while receiving treatment with liver extracts are described. The relapses were probably due to the low vitamin-B_{12} content of the liver extracts. Attention is drawn to the poor vitamin-B_{12} content of most liver extracts, and the practical importance of this is emphasized.

We are grateful to Dr. J. A. W. McCluskie for advice and criticism; to Professor E. J. Wayne for facilities in his department; to Dr. E. Lester Smith, of Glaxo Ltd., for the gift of ^{57}Co B_{12}; and to Dr. W. L. Williams, of Lederle Inc., New York, for the gift of intrinsic factor.

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Medical Memoranda

A Small Outbreak of Bornholm Disease in the Gambia

Since Sylvest (1934) gave a full description of the recorded outbreaks of Bornholm disease up to 1931, there have been many reports of further outbreaks from different parts of the world. The only previous report from West Africa we could find was by Colbourne (1954), who recorded a small outbreak in the Gold Coast (Ghana) with limb pains as the predominant feature. We record here a small outbreak of the disease in a European community in the Gambia, West Africa.

The four cases all occurred in November, 1956, in Fajara, a mainly European residential area 9 miles (14.5 km.) along the coast from Bathurst, the capital town. All the patients had been in the Gambia for at least six months.

CASE REPORTS

Case 1.—A European woman aged 30 complained of severe pain of sudden onset in the lower part of the anterior thorax on the right side. Her temperature varied between 101 and 103° F. (38.3 and 39.4° C.). She was admitted to hospital, given symptomatic treatment, and discharged after three days. During that time no localizing physical signs in the lungs, pleura, or abdomen were found. Her W.B.C. was 10,000/c.mm. with a normal differential count. Her thick blood film was negative for malarial parasites. Three days after her discharge from hospital she had a second and even more severe attack of pain affecting the left side of her chest in a comparable position to her first attack. The pain was very acute and spasmodic in character, and was aggravated by coughing, yawning, and sneezing. She also complained of frontal headache. Her temperature in this attack varied between 103 and 104° F. (39.4 and 40° C.). On examination moderate tenderness and hyperaesthesia were found over the left lower intercostal muscles. Her symptoms subsided gradually and cleared in three days, no specific treatment having been given again. Three weeks after her illness (30 days after the onset of the first attack), when she was in good health, her blood was tested for the specific neutralizing antibodies to the five types of group B Coxsackie viruses (Dalldorf, 1952) and showed neutralizing antibodies to four of them. This being a single convalescent serum, however, no definite laboratory confirmation could be obtained.

Case 2.—The husband of the first patient, a European aged 32, three days after his wife's first attack suddenly experienced the onset of severe spasmodic pain in the region of the xiphisternum which lasted 36 hours. He was admitted to hospital, where his temperature was found to vary between 101 and 102° F. (38.3 and 38.9° C.). No localizing physical signs were found and his W.B.C. was 9,400/c.mm., with a normal differential count. No malarial parasites were found in the thick blood film. He was given analgesics and discharged after three days. Blood taken three weeks after his illness showed neutralizing antibodies to four of the five types of group B Coxsackie viruses tested. This also being a single convalescent serum, no definite laboratory confirmation of the diagnosis could be obtained.

Case 3.—A week after the occurrence of Case 2 a European man aged 40 had sudden onset of pain in the right lower intercostal muscles, described by the patient "as if I had been kicked in the ribs during a Rugger match," and accompanied by profuse sweating. On examination his temperature varied from 100 to 101° F. (37.8 to 38.3° C.). There was moderate tenderness but no hyperaesthesia over the affected area. The illness lasted three days, during which time he was not sent to hospital, remaining ambulant except for the first 24 hours. During his illness the W.B.C. was 8,900/c.mm., with a normal differential, and the thick blood film was negative for malarial parasites. Serum taken on the third day of his illness, and again 20 days later, and sent for neutralization tests in tissue culture (monkey kidney), with the five types of group B Coxsackie viruses, failed to give any evidence of recent infection with these viruses.

Case 4.—On the same day as in Case 3 a European man aged 37 experienced a sudden onset of severe pain in the right lower intercostal muscles, which he described as if a brass plate were being screwed into him. On examination his temperature varied between 101 and 103° F. (38.3 and 39.4° C.) and there was marked tenderness over the site of the pain, although no hyperaesthesia could be elicited. His W.B.C. was 10,000/c.mm., with a normal differential, and a thick blood film contained no malarial parasites. His illness lasted three days, during which time only analgesics were given. Serum taken during his convalescence (three weeks after the acute attack) and tested for neutralizing antibodies to the five types of group B Coxsackie viruses gave no evidence of recent infection with these viruses.

COMMENT

One or two interesting points about these four cases include the fact that all the attacks (five in four patients) lasted three days, all the patients were aged 30–40 years, and despite the fact that two of them had young children none of these developed an attack. All the patients had the pain in the same site—the lower intercostal muscles—whereas the cases described by Colbourne from the Gold Coast experienced the pain mainly in the limb muscles.

Although in the one case where acute and convalescent serum were available (Case 3) no serological evidence of recent infection with the group B Coxsackie

viruses was obtained, the clinical picture throughout was so typical that we cannot attribute the symptoms to anything but Bornholm disease.

We thank Dr. Ian A. McGregor for permission to publish, and Dr. T. Langwell, superintendent of the Victoria Hospital, Bathurst, for referring two of the cases to us. We are grateful to Dr. K. E. K. Rowson, of the Central Public Health Laboratory, Colindale, London, for performing the serological tests.

R. D. FOORD, M.B., B.S.,
H. M. GILLES, M.D., B.Sc., D.T.M.&H.,
Medical Research Council Laboratories, Fajara, Gambia, British West Africa.

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Repeat Hydatidiform Mole, Presumed Second Mole, Occurring within Twelve Months

The incidence of hydatidiform mole has been estimated as being between 1 in 2,500 (Novak, 1952) and 1 in 610 (Moore *et al.*, 1957). The increased incidence in recent years may be a true increase or may be due to a greater amount of abortion material being examined. The incidence of repeat mole is less easy to determine. Brews (1939) found 1 repeat mole in a series of 100 cases of hydatidiform mole; Chesley *et al.*, (1946) found 1 in 57; Jeffreys and Graffagnino (1944) found 2 in 28. Other cases have been reported by Mathieu (1937), Wall and Hertig (1948), Jaikaran (1955), and Posner *et al.* (1955). Repeat mole within one year of the first must be extremely rare.

CASE REPORT

A married woman aged 33 was admitted to hospital on July 22, 1955. Her previous health had been good. She had had two previous pregnancies; the first, four years previously, had been uneventful, ending in a normal delivery at home; the second, two years later, had ended in a spontaneous abortion at three months. Her last normal menstrual period had been 12 weeks prior to admission, on May 4. She had been perfectly well until 15 days before admission, when she had had excessive vomiting, occurring at any time of the day, and daily slight bleeding per vaginam. She had also noticed that there had been a fairly rapid increase in the size of her abdomen accompanied by backache and generalized abdominal discomfort.

On admission she was pale; her blood pressure was 145/90, pulse 100, and temperature normal. The uterus was enlarged to 2 in. (5 cm.) above the umbilicus, and was tense and tender. *X*-ray examination failed to show foetal parts. A Hogben test was reported as positive undiluted, but not strong enough to warrant diluting. Vaginal bleeding continued to be slight and the uterus to increase in size. The haemoglobin fell to 30% (4.3 g./100 ml.), so she was given 4 pints (2,160 ml.) of blood over the next two days.

On August 8, 16 days after admission, she aborted a hydatidiform mole which was estimated as 2 pints (1,080 ml.) of vesicles and 1 pint (540 ml.) of old blood. The vesicles varied in size from 2 mm. to 2 cm. After this she received a course of penicillin and sulphadimidine for a low-grade pyrexia. On August 18, 10 days after aborting, she was examined in the operating theatre under general anaesthesia, and a thorough curettage was performed. The uterus was firm and the cavity smooth. The right ovary was slightly enlarged and felt cystic. The curettings were examined histologically and reported on as follows: "Degenerated and infected decidua present; no chorionic structures identified." A further Hogben test was reported as negative, and, as her haemoglobin was now 61% (8.8 g./100 ml.), she was discharged from hospital at the end of August.

When seen in the out-patient department in September she had had a normal period. The uterus was normal in size and the right ovary only slightly enlarged. As the Hogben test was reported as negative she was asked to return to the clinic in early December. When she did so she had had three normal periods, the last one being five weeks previously. She did not think that she was pregnant, although there was a possibility that she might be. Examination was inconclusive. A Hogben test performed during the next week was weakly positive undiluted. A further specimen of urine one week later was also reported as positive undiluted, with too weak a reaction to warrant dilution. Shortly after this, on January 14, 1956, she attended the out-patient department complaining of a sudden severe painless bleeding following 12 weeks' amenorrhoea. She admitted the possibility of further pregnancy, and was taken into hospital for observation. As the bleeding continued it was decided to empty the uterus.

Two days after admission this was done under general anaesthesia, when, on dilating the cervix, typical vesicles of hydatidiform mole escaped. The uterus was emptied and a curettage performed. Histological report of the curettings was: "Hydatidiform mole. The trophoblast is fairly active-looking, but no malignancy is seen." A Hogben test 12 days after evacuating the uterus was positive; eight days later it was negative. The test was repeated monthly for the first three months after she went home, and then at gradually increasing intervals, and has remained negative. Her menstrual cycle was regular, and repeated clinical examinations have revealed no abnormality.

COMMENT

In this case the occurrence of a second hydatidiform mole so soon after evacuation of the first raised the problem of whether this was growth of mole remaining from the first instance or a true second mole. The negative curettage, negative Hogben test, and normal menstrual cycle made the latter diagnosis tenable. In half the cases reported in the literature, treatment of the second mole was by evacuation of the uterus, in the remainder by hysterectomy. In this case the patient is anxious to have another child, and it was felt that hysterectomy was not justifiable.

This case was first presented at a meeting of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine held on January 25, 1957. My thanks are due to Miss E. D. M. Wilson, under whose care this patient was admitted, for permission to record this case and for her encouragement and advice in the preparation of the paper.

DOROTHY M. GRATTON, M.B., Ch.B., M.R.C.O.G.,
Late Obstetric and Gynaecological Registrar, St. Helier Hospital, Carshalton, Surrey.

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Reviews

LORD ADDISON

Viscount Addison: Leader of the Lords. By R. J. Minney. (Pp. 256; illustrated. 25s.) London: Odhams Press. 1958.

This Life of Lord Addison, as might be expected from the author of *Clive of India*, is an interesting one. It is based on Lord Addison's own papers, family diaries, and the Lloyd George papers lent by Lord Beaverbrook, and may be considered the official biography. As its title implies, it is mainly concerned with Addison the statesman. The first seven chapters deal with the zenith of his career as Leader of the House of Lords, and it is not until page 99 that we come to his earlier years. With this wealth of material, Mr. Minney has been able to devote only a few pages to his subject's medical attainments. Yet these attainments are of the utmost significance in Addison's life. For it was his knowledge of medicine, medical research, and public health that enabled him to guide Liberal and Labour Governments in their health and social legislation on the right lines; and to teach Ministers not to ignore the advice of leaders of the profession in these matters.

Christopher Addison came of yeoman farming stock and was born at Hogsthorpe, Lincolnshire, on June 19, 1869. Subsequently the family moved to Stallingborough, from which place the future peer was to take his title. Throughout his life he retained his Lincolnshire accent and was proud of it. Addison's student period at St. Bartholomew's Hospital culminated in the M.D. London and the F.R.C.S. As soon as he could manage it he repaid his father the whole cost of his medical education. He specialized early in anatomy, and by 1897 held the first chair of anatomy in the University of Sheffield. In addition to examining at the University, he examined for the Primary Fellowship of the Royal College of Surgeons. A colleague said: "Addison's courtesy in ascertaining a candidate's knowledge of anatomy was only equalled by the politeness with which he dismissed those who failed to attain a high standard." In 1901 he was Hunterian Professor at the Royal College of Surgeons, and returned to London, becoming lecturer on anatomy, first at Charing Cross Hospital Medical School and in 1906 at St. Bartholomew's Hospital. His discovery of "Addison's transpyloric plane" and his papers and books on anatomy made him a leading authority on the subject.

As other British anatomists have done—Sir William Petty, Sir John Finch, Sir Walter Foster (Lord Ilkeston), and Sir Auckland Geddes (Lord Geddes)—Addison now turned to politics. In 1910 he was elected Liberal M.P. for Hoxton. His knowledge of medicine, his tact and diplomacy, were of inestimable value to Lloyd George in passing the National Insurance Act in 1911. Addison conciliated the medical profession and induced doctors to accept new conditions of practice that at first were strange and repugnant to them. He was a successful Minister of Munitions from 1916 to 1917, and in 1919 became the first Minister of Health. His fertile brain had many plans for improvement of the public health and social welfare, including reform of the poor law. But housing was the paramount need, for Lloyd George had promised "homes for heroes." Addison did his best, but his advisers' schemes were expensive, prices soared, and the cost of materials and labour became prohibitive. Mr. Minney shows that Addison's removal was an unjust and shabby business.

It should be remembered that Addison had a large share in the formation of the Medical Research Committee, and it was due to him that on the advice of Sir Walter Fletcher and Sir Robert Morant the Medical Research Council was constituted after the first world war as a committee of the Privy Council and not merged in the Ministry of Health. In after-days as Lord President of the Council he continued to encourage and aid medical research.

Addison went into retirement, and wrote his autobiography in two volumes and various books on social problems. He joined the Labour Party, became M.P. for Swindon, and returned to office in 1929 in Ramsay MacDonald's second Ministry as Parliamentary Secretary to the Minister of Agriculture. He was Minister of Agriculture in the succeeding two years with credit and success. From 1931 to 1937 he was again out of Parliament. Persuaded by Mr. Attlee to accept a peerage in 1937, Addison became Leader of the House of Lords in 1945 at the age of 77, and was able to put through the entire Labour programme "punctually and without sacrifice of essentials," as he said. The credit for this was due to his integrity, tact, and skill, and was shared by Lord Salisbury, his political opponent, who helped to avoid a major clash between the Upper and Lower Houses until the final tussle on the nationalization of iron and steel. Addison won the respect and affection of the entire House.

Lord Addison received from King George VI the Order of the Garter for his conspicuous services. He was the first medical man to obtain this high award, and at the time was overcome by the unexpected honour. He died on December 11, 1951, in his 83rd year.

Mr. Minney's biography depicts a statesman of rare qualities and brings out Addison's innate goodness, kindness, and modesty. He bore failure and success with equanimity, and had a high sense of vocation in both professional and political life.

ARTHUR S. MACNALTY.

DICTIONARY OF PSYCHOLOGY

A Comprehensive Dictionary of Psychological and Psychoanalytical Terms. A Guide to Usage. By Horace B. English and Ava Champney English. (Pp. 594+xiv. 60s.) London: Longmans, Green and Co. 1958.

Those who battle their way through the steadily increasing barrage of denominational textbooks on psychology are sooner or later driven to the conclusion that the most reliable of them all is a standard etymological dictionary, not simply because of the dependable definitions of basic terms it affords, but because the history of words is in fact the history of psychology. Horace English, a psychological lexicographer of international repute, has gone a step further and has produced a guide to terminological usages for readers and writers in the fields of psychology, psychoanalysis, psychiatry, education, guidance, and social work. Here is a "defining dictionary," a collection of meanings interspersed with lively critical glosses, the whole being intended to eliminate confusions so far as that is possible in a tangle of confused and as yet larval sciences.

It is a tribute to the editor's tidy-mindedness, his common sense and balance of judgment, and to his erudition that he has achieved his aims to a remarkable degree. Testing its accuracy in one field alone—namely, that of psycho-analysis—the book can scarcely be

faulted, except perhaps in its general definition by which the author (no doubt resigning himself to American eclecticism) includes under the term "analytical psychology" individual psychology and other fundamental deviations from orthodox psychoanalysis. This at first sight is calculated to send the Freudian analyst puce, as will also his view that "repression" can no longer be restricted to its original Freudian connotation. Nevertheless, throughout the text he does fairly distinguish Freudian from Jungian and Adlerian concepts.

In other respects Mr. English has cast his net widely, and, so far as this reviewer can judge, with accurate aim. Sometimes he is not above including a slang expression. A *psychoceramic* (an abominable neologism at any time) is defined as a "crackpot" or a person suffering from mental illness. And both psychologists and psychiatrists will enjoy his admonition, "just as psychologists should not, and do not, claim to be psychiatrists"—a statement incidentally which is no longer accurate, in Great Britain at any rate—"so psychiatrists should not call themselves psychologists"—a somewhat summary injunction at which clinical psychologists may fairly demur. These minor matters aside, the book can be described as a public psychological service. There are not many psychological works that deserve the hackneyed encomium "This volume should be on every bookshelf." Mr. English's dictionary certainly does; it should indeed lie open on every psychologist's desk, if not on his bed-table.

EDWARD GLOVER.

NEURITIS AND NEURALGIA

Neuritis, Sensory Neuritis, Neuralgia. A Clinical Study with Review of the Literature. By Robert Wartenberg, M.D. Foreword by Wilfred Harris, M.D. (Pp. 444+xii; illustrated. 68s.) New York and London: Oxford University Press. 1958.

The author never lived to see this book through the press. Topics relating to the more distal parts of the nervous system always appealed to him rather than problems of higher cerebral dysfunction. Wartenberg used to exhort his students over and over again to "think peripherally." Despite his idiosyncrasies Wartenberg was a hero-worshipper, and he held in particularly high esteem Dr. Wilfred Harris, who has been good enough to furnish a foreword. Wartenberg always held strong and sometimes unorthodox views upon terminology, and in this book he has expressly avoided utilizing the topical expression "neuropathy," favouring the older version "neuritis." Another of Wartenberg's dislikes was the employment of eponymous terms in neurology. In this volume he has gone even farther, by excluding, so far as he could, proper names from the text. He does so by recourse to the device of using such roundabout phrases as "it has been said . . ." or "one author describes . . ." and then inserting figures which refer to a bibliography appended to each chapter. Some readers may well look upon this as an unnecessary, and even irritating, antic. The subject-matter of this monograph is entirely clinical in its scope, and didactic; and it is presented in a breathless fashion. The number of references given is great indeed. One of Wartenberg's conclusions reads: "It is impossible to say anything new regarding the problem of neuritis-neuralgia. Everything has been said, forgotten, and said again." Consequently it is not easy to decide at what type of audience this book is directed.

MACDONALD CRITCHLEY.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received

The Wastes of Civilization. By J. C. Wylie. (Pp. 160. 16s.) London: Faber and Faber. 1959.

Chronische Krankheiten des Bindegewebes. Beiträge zur Pathologie und Klinik der Organ- und Systemsklerosen. By Professor Dr. Rolf Emmrich. (Pp. 280+ix; illustrated. DM. 41.60.) Leipzig: VEB Georg Thieme. 1959.

Le Médecine Légale Judiciaire. By Jean Planques. (Pp. 127.) Paris: Presses Universitaires de France. 1959.

An Outline of Human Relationships. By Eustace Chesser. With a Preface by Sir Cyril Burt. (Pp. 446. 25s.) London: Heinemann. 1959.

The Middle Ear. By Heinrich G. Kobrak. Foreword by John R. Lindsay. (Pp. 254+xvi; illustrated. £5 12s. 6d.) Chicago: University of Chicago Press. London: Cambridge University Press. 1959.

Practical Obstetric Problems. By Ian Donald, M.B.E., M.D., B.S.(Lond.), B.A.(Cape Town), M.R.C.S.(Eng.), L.R.C.P.(Lond.), F.R.F.P.S.(Glasg.), F.R.C.O.G. Second edition. (Pp. 712+xvi; illustrated. 55s.) London: Lloyd-Luke (Medical Books) Ltd. 1959.

Tumors of the Lungs and Mediastinum. By B. M. Fried, M.D., F.C.C.P. (Pp. 467; illustrated. £5.) London: Henry Kimpton. 1959.

Diagnostic des Lésions Intra-Craniennes par les Radio-Isotopes. (Gammaencéphalographie.) By Thérèse Planiol. (Pp. 253+vii; illustrated. 5,000 fr.) Paris: Masson et Cie. 1959.

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BRITISH MEDICAL JOURNAL
LONDON
SATURDAY MARCH 28 1959

ANTICOAGULANTS FOR MYOCARDIAL INFARCTION

The value of treatment with anticoagulants during the first four weeks after acute myocardial infarction is now established. When J. A. Tulloch and A. R. Gilchrist[1] reported the first controlled series studied in Britain they were able to confirm earlier reports,[2–5] notably those of I. S. Wright and his colleagues, that anticoagulant therapy reduces the mortality rate by approximately one-half. Subsequently there have been many similar and confirmatory studies, and anticoagulants are now used as a routine in many British hospitals for the treatment of patients in the acute phase of myocardial infarction. In contrast, the value of continuing to administer anticoagulants for months after myocardial infarction was not established. But the Medical Research Council's study, published in the opening pages of this week's *Journal*, now provides evidence that anticoagulants can benefit some patients when administered during the months after the acute phase.

The object of this report on 383 patients studied at 15 centres was to establish whether, "in patients who had survived at least one month after their most recent infarction, the continuous administration of an anticoagulant drug (phenindione) in doses sufficient to double the one-stage 'prothrombin' time would appreciably reduce the risk of recurrence and death below the levels concurrently observed in a series of patients with illness of comparable severity not thus treated." Patients vary greatly, and so does the course of this disease; it was therefore essential that the criteria for inclusion in such a trial should lead to as much uniformity as possible between groups to be compared. This has been achieved to some extent by confining the study to patients between the ages of 40 and 69 years recovering from a recent transmural myocardial infarct, with Q-wave evidence of infarction in the electrocardiogram, and excluding patients with intramural myocardial infarction, uncontrolled heart failure, malignant hypertension, cerebral vascular accidents, peptic ulceration, hepatic disease, and other diseases associated with a high morbidity. These fairly strict criteria excluded two-thirds of the patients diagnosed and treated as cases of myocardial infarction by the physicians co-operating in this study. The remainder were classified according to the number of previous infarcts, and then, within these infarct classes, assigned at random into two groups. One group received phenindione in doses which increased the one-stage prothrombin time to between 2 and 2½ times the control level (high-dosage group), and the other group received outwardly similar tablets containing insufficient phenindione (1 mg.) to influence the one-stage prothrombin time (low-dosage group). Patients in the low-dosage group attended hospital for regular estimations of prothrombin time and clinical assessment in exactly the same way as those in the high-dosage group.

While the selection of patients must necessarily limit the conclusions which can be drawn from this trial, two main findings emerge. In men, long-term anticoagulant therapy reduced the mortality during the first three months of its administration, but not significantly thereafter. In men, anticoagulants reduced the incidence of further infarction throughout the two years of the study. Under the age of 55, infarction recurred at only one-fifth of the rate observed in the low-dosage group, and over that age the reinfarction rate was halved. The trial affords no evidence that continued anticoagulant therapy was of benefit to the women patients.

After the first three months the high-dosage group probably included patients who would otherwise have died, and therefore any reduction in the reinfarction rate might be expected to underestimate the benefit of such treatment. Nevertheless, it is disappointing that reduction in the rate of further infarction was not associated with a significant decrease in the overall mortality rate. To gain a more clear-cut conclusion a greater number of cases in the trial would have been preferable, but that can be difficult to arrange.

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[3] Wright, I. S., *Amer. Heart J.*, 1946, **32**, 20.
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[5] Wright, I. S., Marple, C. D., and Beck, D. F., ibid., 1948, **36**, 801.
[6] Manchester, B., *Ann. intern. Med.*, 1957, **47**, 1202.
[7] Bjerkelund, C. J., *Acta med. scand.*, 1957, **158**, suppl. 330.
[8] Peel, A. A. F., *Brit. Heart J.*, 1955, **17**, 319.
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[10] Westlund, K., and Hougen, A., *Acta med. scand.*, 1956, **154**, suppl. 315.
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[16] Sougin-Mibashan, R., and Horwitz, M., *Lancet*, 1955, **1**, 1191.
[17] Gilchrist, A. R., and Tulloch, J. A., *Scot. med. J.*, 1956, **1**, 1.
[18] Mintz, S. S., and Katz, L. N., *Arch. intern. Med.*, 1947, **80**, 205.

The Medical Research Council's trial supports B. Manchester's finding[6] that protection from reinfarction lasts several years. In his 10-year study the recurrence rate was more than halved, and this reduction was most marked during the first two years of treatment. The trial also supports C. J. Bjerkelund's observations[7] that anticoagulants reduce mortality only during the first few months of treatment and that protection from reinfarction and cardiac failure was most evident in younger males. The prognosis after myocardial infarction has often been reported[8–10] to be better in younger patients, and it might be argued that anticoagulants would be more likely to benefit patients with the least extensive myocardial and coronary disease. Moreover, young patients with myocardial infarction have high plasma levels of lipid more commonly than older patients,[11] and their metabolism may therefore be different. Several authors[12–17] have suggested that the benefits of anticoagulants may not depend solely on their powers to prevent intravascular clotting, and the metabolic effects of these drugs require more investigation.

The lack of effect of long-term anticoagulants on rates of mortality or reinfarction in women might be a reflection of their greater age and worse prognosis,[7 18] but the present findings agree with Bjerkelund's conclusion derived from a numerically comparable group that in women continued anticoagulant therapy does not influence mortality. This difference between the sexes remains unexplained and may be another indication that anticoagulants have other effects than reducing the tendency to form intravascular thrombi.

Continued anticoagulant therapy is not always practicable and is a constant burden for the doctor and the patient. Indeed, if it is to succeed, the patient must be reasonably intelligent and be prepared to attend hospital regularly. It is seldom justifiable to allow more than four or five weeks to elapse between estimations of prothrombin time. Both the British and Norwegian[7] studies indicate that haemorrhage is six times more common when anticoagulants are administered. The Medical Research Council's trial was conducted in highly specialized units where close attention was given to its management. The risk of haemorrhage may therefore be greater elsewhere, and it is important to stress that the patient's prothrombin time should be estimated regularly in a reliable laboratory.

Although the criteria of selection for this trial excluded about two-thirds of patients usually diagnosed as suffering from myocardial infarction, one conclusion can be reached with confidence. Men who experience severe myocardial infarction before the age of 55 can be expected to benefit from the continuation of anticoagulant therapy for six months after the infarct. No definite recommendations can yet be made for older men, and further studies are needed of the benefits of anticoagulants beyond a period of six months; more study is also needed of their effects on women and on men with minor infarcts. The results of this trial suggest that the demands on the time of doctors, nurses, and technicians are likely to increase, perhaps considerably, if the facilities for long-term anticoagulant therapy are to be adequate. Foreseeing the likelihood of this, the Government health departments have for some time wisely encouraged hospital boards to expand their provisions for controlling anticoagulant therapy.

AETIOLOGY OF DISSEMINATED SCLEROSIS

The principal clinical and pathological features of disseminated or multiple sclerosis have now been recognized for over 100 years, but our ignorance of its aetiology remains profound. There can be few disorders for which so many theories of causation have been propounded. Many which once appeared reasonable according to views on the aetiology of disease then current now seem illogical or even absurd. Nevertheless, as Drs. H. Miller and K. Schapira point out in a comprehensive review in the *Journal* of this and last week (pp. 737 and 811), none of the popular modern theories can be regarded as proved, even though the many new facts gathered about this and related disorders have stimulated research on the problem.

1 *Brit. med. J.*, 1958, **2**, 1025.
2 McAlpine, D., ibid., 1957, **1**, 475.
3 Sutherland, J. M., *Brain*, 1956, **79**, 635.
4 Pratt, R. T. C., *Ann. Eugen. Lond.*, 1951, **16**, 45.
5 Thums, K., *Wien. Z. Nervenheilk.*, 1951, **4**, 173.
6 Mackay, R. P., and Myrianthopoulos, N. C., *Proceedings of the Sixth International Congress of Neurology*, 1957, Sect. 8, **10**, Suppl., p. 24.
7 Smith, H. V., Espir, M. L. E., Whitty, C. W. M., and Russell, W. R., *J. Neurol. Neurosurg. Psychiat.*, 1957, **20**, 1.
8 Leyden, E., *Die graue Degeneration der hinteren Rückenmarksstränge*, 1863, Berlin.
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10 Swank, R. L., *Arch. Neurol. Psychiat.* (*Chicago*), 1953, **69**, 91.
11 —— ibid., 1953, **69**, 281.
12 Campbell, A. M. G., Daniel, P., Porter, R. J., Russell, W. R., Smith, H. V., and Innes, J. R. M., *Brain*, 1947, **70**, 50.
13 —— Herdan, G., Tatlow, W. F. T., and Whittle, E. G., ibid., 1950, **73**, 52.
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15 Brickner, R. M., ibid., 1952, **68**, 180.
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18 Yahr, M. D., Goldensohn, S. S., and Kabat, E. A., *Ann. N.Y. Acad. Sci.*, 1954, **58**, 613.
19 Uchimura, I., and Shiraki, H., *J. Neuropath. exp. Neurol.*, 1957, **16**, 139.
20 Pette, H. *Dtsch., Z. Nervenheilk.*, 1928, **105**, 76.
21 Ferraro, A., *J. Neuropath. exp. Neurol.*, 1958, **17**, 278.

Any theory of aetiology must explain the remarkably diverse clinical features of the disease and its remittent course, its variable geographical distribution, its failure to follow a distinct hereditary pattern despite an apparent inherited element, and its liability to relapse in response to many different factors. As was pointed out in these columns recently,[1] there is now a great deal of evidence to suggest that the disease may occur in a very mild form, with prolonged remissions, often of several years, separating slight episodes of neurological disability. Cases of this type are more frequent than is generally realized.[2] Yet there are many others in which the progress of the disease is rapid and unrelenting, and we have no reliable evidence to indicate why this should be so. Nor do we understand why the condition should be rarer in tropical countries than in those with a cold or temperate climate. Again, in areas of relatively uniform climate, islands of increased incidence of the disease are found which seem not to be entirely accounted for by inbreeding.[3] It is also difficult to understand why there are so many reported instances of the disease in only one member of a pair of identical twins[4-6] despite the fact that the disease occurs more often in several members of a family than could be accounted for by chance.[2] Miller and Schapira report a particularly striking family in which one member of an identical twin pair, and several other members of the family, were affected, yet the other twin was normal. Clearly, therefore, the genetic influence is not very strong, but the comparative rarity of conjugal cases makes it unlikely that the familial incidence can be accounted for by contagion or infection. Another relationship observed but not explained is that between episodes of disseminated sclerosis and trauma, infective illness, and emotional stress. A hypothesis incriminating allergy may explain the occurrence of symptoms after infection or prophylactic inoculation, and it is now apparent that temporary exacerbation of the disease may follow an artificially induced inflammatory response in the central nervous system[7]; nevertheless, relapse after trauma, which has been reported before,[8 9] and is typified by case 501 of Miller and Schapira, is much less easily explained.

Of the aetiological theories now current, those implicating a high intake of dietary fat[10 11] or heavy metals,[12 13] venous thrombosis,[14] or vasospasm[15] have few adherents. There remain two principal views. The first is that the disease is due to a specific infection by a spirochaete, a virus, or some as yet unidentified micro-organism; the second that it is due to an allergic or hypersensitivity response in the nervous system. Though the theory of specific infection still has adherents, since frequent claims are made that the responsible agent has been isolated, the repeated failure of such claims to stand detailed scrutiny, and the inability of many competent bacteriologists and virologists to isolate an organism from affected patients and pathological material, have increasingly cast doubt on the validity of this view. This does not mean that the theory is necessarily untenable, for there are other diseases, including encephalitis lethargica and benign myalgic encephalomyelitis,[16] which seem likely to be due to virus infection but in which the causal organism remains unidentified. But for disseminated sclerosis it does seem to be improbable.

As Miller and Schapira indicate, there is, on the other hand, much evidence to suggest that the disease is due to a "characteristic pathological response in the nervous system, variable in localization and tempo, and in some way related to a disturbance in the balance of immunity and allergy." This opinion receives modest support from recent work which has shown that the gamma-globulin in the cerebrospinal fluid is raised in such cases,[17 18] while the reaction to intrathecal tuberculin is modified and resembles that occurring in the cortisone-treated animal.[7] This theory would also explain the common initiation or exacerbation of disseminated sclerosis after non-specific infection and inoculation, as Miller and Schapira describe. Further support comes from the close relationship which appears to exist between disseminated sclerosis on the one hand and acute disseminated encephalomyelitis on the other. The latter disease, and its more explosive variants, acute haemorrhagic leucoencephalitis and brain purpura, are now accepted as hypersensitivity diseases, occurring as they do after a variety of exanthemata, non-specific infections, or prophylactic inoculations. They also resemble very closely the experimental allergic encephalomyelitis in animals which can be produced by a variety of allergens. It is true that the pathological changes in these allergic disorders (perivascular cellular infiltration and demyelination) are broadly similar to those observed in disseminated sclerosis, in which demyelination is often perivenous or periventricular in distribution but in which collections of inflammatory cells are rarely seen. Furthermore, the clinical and pathological features of the neurological syndrome which occasionally follows rabies inoculation[19] are remarkably reminiscent of those seen in disseminated sclerosis. But, despite these similarities, there are certain distinct differences; thus disseminated encephalomyelitis is usually a self-limiting disease which is not liable to

recur, and the therapeutic response to steroid therapy seems often to be excellent in encephalomyelitis but is singularly unpredictable even in acute cases of disseminated sclerosis. One serious difficulty, to which Miller and Schapira draw attention, is that there is at present no satisfactory definition of disseminated sclerosis, and, both clinically and pathologically, acute forms of this condition seem to overlap varieties of encephalomyelitis. Yet they may be entirely different diseases aetiologically, for the nervous system's repertory of pathological responses seems remarkably limited when studied with conventional histological techniques. Hence it is not yet possible to accept without reservation the unitarian views of H. Pette[20] and A. Ferraro,[21] according to which disseminated sclerosis and acute disseminated encephalomyelitis are regarded as varying manifestations of an allergic response by the nervous system. Even if this theory was established, it would still be necessary to identify the many allergens which could cause episodes of disseminated sclerosis, the mechanisms by which they produce their effects, and the constitutional factors which might make it more easy for them to do so. It seems clear that further inquiry on immunological lines will lead to an elucidation of many of the secrets of the disease.

LIVER EXTRACTS AND PERNICIOUS ANAEMIA

A commonly repeated pattern in the history of therapeutics is the discovery of some pharmacological action in an extract of vegetable or animal origin, the subsequent isolation from this extract of the active principle, the elucidation of its chemical structure, and often, as a final stage, its synthesis. It is generally accepted doctrine that, when it becomes available, the pure chemical substance should be used in treatment rather than the complex from which it was originally isolated. These extracts are frequently of inconstant composition, and precision of dosage is possible only when the active principle can be prescribed.

The isolation of vitamin B_{12}, or cyanocobalamin, has followed these steps. The story is familiar to all: the discovery of the efficacy of liver, and later of liver extracts, in the treatment of pernicious anaemia and the eventual success of the prolonged struggle to wrest from these extracts the active anti-anaemic principle. Liver extracts are of variable composition and there is no reason to suppose that they contain any haematinic factors other than vitamin B_{12} and, in the cruder extracts, folic acid. It is known that pernicious anaemia is the result of a conditioned deficiency of vitamin B_{12} and that nothing apart from the vitamin is required for its relief.

All physicians with a particular interest in the treatment of patients with this disease renounced liver extracts immediately preparations of the pure vitamin became available: they have long been convinced that there is now no place for liver extracts in therapeutics. This opinion is forcibly endorsed by a paper from Dr. J. F. Adams and Dr. G. C. Timbury in this number of the *Journal* (p. 833). They report the history of two patients with pernicious anaemia who relapsed and developed subacute combined degeneration of the cord while receiving treatment with liver extracts. In both cases microbiological assay proved the extract to contain infinitesimal quantities of vitamin B_{12}—0.09 μg. and 1.5 μg. per ml. respectively. It is clear that relapse occurred in each case because the vitamin-B_{12} content of the liver extract used was grossly inadequate. The authors review twenty liver extracts commonly used in this country and point out that, even when the manufacturers' claims for their vitamin-B_{12} content are assumed to be correct, the doses recommended are, except in one extract, quite inadequate for the safe treatment of pernicious anaemia. Moreover, the cost of maintenance, even in the doses recommended, is considerably in excess of the cost of adequate treatment with crystalline vitamin B_{12}.

It may surprise some to learn that liver extracts are still used in the treatment of this disease. This article proves that they should not be. Whether they even now serve any useful therapeutic purpose is doubtful, but it is certain that in the management of patients with pernicious anaemia their use is not merely of inconstant efficacy and excessive cost, but often of positive danger.

HAEMOLYTIC REACTIONS TO DRUGS

Haemolysis is a well-recognized complication of the administration of some drugs, and phenylhydrazine was for long used in treating polycythaemia on account of this action. If haemolysis is severe haemoglobinuria may occur and anaemia develop, but if it is mild the process may not be noticed unless sensitive methods of detection are used. Phenacetin has not been incriminated as a cause of haemolysis until recently, but three reports from Switzerland[1 2 3] strongly suggest that such a complication may sometimes be overlooked.

In the first of these papers H. R. Marti[1] describes 70 cases of chronic phenacetin overdosage in patients who were taking between 1 and 10 g. of the drug daily. Half of these had haemoglobin concentrations of less than

[1] Marti, H. R., *Schweiz. med. Wschr.*, 1958, **88**, 1054.
[2] Miescher, P., and Pleischer, A., ibid., 1958, **88**, 1056.
[3] Pletscher, A., Studer, A., and Miescher, P., ibid., 1958, **88**, 1214.
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[6] Harris, J. W., *J. Lab. clin. Med.*, 1956, **47**, 760.
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[8] Dern, R. J., Beutler, E., and Alving, A. S., ibid., 1955, **45**, 30.
[9] Schrier, S., Kellermeyer, R., Carson, P., and Alving, A. S., ibid., 1957, **50**, 951.
[10] Steinberg, A., Sheba, C., Hirshorn, N., and Bodonyi, E., *Blood*, 1957, **12**, 603.
[11] Kimbro, E. L., Sachs, M. V., and Torbet, J. V., *Bull. Johns Hopk. Hosp.*, 1957, **101**, 245.
[12] Zinkham, W. H., and Childs, B., *J. clin. Invest.*, 1957, **36**, 938.
[13] Gross, R. T., Hurwitz, R. E., and Marks, A. A., ibid., 1958, **37**, 1176.
[14] Beutler, E., *J. Lab. clin. Med.*, 1957, **49**, 84.
[15] Meulengracht, E., and Lundsteen, E., *Folia haemat.* (*Lpz.*), 1939-40, **63**, 89.
[16] Hall, B. E., Pfuetze, K., Hinshaw, H. C., and Feldman, W. H., *Proc. Mayo Clin.*, 1942, **17**, 24.
[17] Young, L. E., Valentine, W. N., and Howland, J. W., *Ann. Int. Med.*, 1946, **24**, 104.
[18] Oltramare, M., *Schweiz. med. Wschr.*, 1953, **83**, 156.

10 g. %, and of these only one-fifth were uraemic, so that renal failure could not have been the cause of the anaemia in all cases. The fact that significant reticulocytosis was present in 15 of these patients suggested that the anaemia was a result of either chronic blood loss or haemolysis. Unfortunately blood loss was not excluded in all the patients, but it is probably fair to conclude that haemolysis was the essential cause of the anaemia if evidence from the other papers is taken into consideration. In view of the variability in the occurrence of anaemia the author concluded that there was an individual factor controlling its occurrence and that its degree of severity was not related to the dose of drug. In a further paper P. Miescher and A. Pletscher[2] determined the survival rate of red cells by the radiochromate method in patients taking 1–2 g. of phenacetin daily. Red-cell survival was reduced in these patients, but not to the extent that would ordinarily have caused anaemia in a patient with a marrow capable of normal compensation. That the reduction in the life span of red cells was due to irreversible cell damage was shown by the shortened life span of the same cells when transfused into healthy drug-free recipients. This fact and an increased urinary excretion of radioactive chromium led to the conclusion that intravascular haemolysis was occurring. The authors point out that, although the rate of haemolysis would not normally cause anaemia, it might well do so in patients with chronic diseases in whom marrow activity was depressed, these being patients most likely to be taking phenacetin continuously. The same workers[3] have studied the effects of phenacetin and its derivatives on the life span of red cells in rabbits and dogs. The doses of drugs used were much greater than the therapeutic doses, but they found that phenacetin, acetamidophenol ("panadol"), and *p*-phenetidine all depressed red-cell survival to an equal extent, suggesting that acetamidophenol, the *in vivo* metabolite of phenacetin which is usually claimed to be less toxic, was not devoid of this damaging effect on red cells.

The evidence from these papers does suggest that haemolysis may occur as a toxic effect of phenacetin, but more work is required to find out if this is a frequent complication of long-continued phenacetin administration in ordinary therapeutic doses. There is no evidence of how the haemolysis occurs. Two processes are known to be involved in haemolytic reactions to drugs. In the first the drug appears to act as a hapten and combines with red cells to render them antigenic. This is probably the mechanism in haemolysis complicating the administration of quinidine[4] and perhaps quinine, methoin,[5] and stibophen.[6] More often thrombocytopenia occurs, but the mechanism causing this appears to be the same.[7] The second process has received much attention since R. J. Dern and his co-workers[8] found that negroes who developed haemolytic anaemia when given primaquine showed an enzyme defect in their red cells which interfered with the normal mechanisms maintaining glutathione in its reduced form. The enzyme was later found to be glucose 6-phosphate dehydrogenase.[9] This defect has now been found in red cells of patients developing haemolysis after taking a number of different drugs: these include sulphonamides and *para*-aminosalicylic acid,[10] nitrofurantoin,[11] and vitamin K analogues.[12] The enzyme defect appears to be transmitted as a sex-linked character[13] and can easily be detected by the glutathione stability test.[14] The way in which glutathione oxidation interferes with red-cell survival remains to be determined. Haemolysis occurring after the administration of other drugs such as acetanilide,[15] glucosulphone,[16] neoarsphenamine,[17] and phenylsemicarbazide ("cryogénine")[18] has also been reported, but the mechanisms leading to this complication have not yet been defined.

DISEASE AND AIR POLLUTION

Even one hundred years ago it was known that mortality in towns was higher than in the country.[1] More recently[2] we have become aware of the enormous toll taken by fog in the metropolis, but E. T. Wilkins[3] has suggested that air pollution regarded as normal causes even more damage, in the long run, both to individuals and to the nation. Nevertheless the amount of direct evidence in favour of this hypothesis has not been large. Difficulty has arisen in finding out which of the many factors associated with living in towns are mainly responsible for the higher mortality.

In 1956 D. D. Reid,[4] discussing death from bronchitis in London, remarked that the interpretation of contrasts in mortality from district to district was extremely difficult. While areas with the highest mortality are the most affected by pollution, they also house the semi-skilled workers and labourers and their families who live in poor and overcrowded houses, and whose work is hard and often associated with exposure to industrial dust and fumes. Authors such as A. T. Gore and C. W. Shaddick[5] and A. S. Fairbairn and D. D. Reid[6] have thought that air pollution was one of the prime factors in the increased mortality from bronchitis, but the latter were unable to show that air pollution contributed appreciably to the increased mortality from lung cancer, as had been suggested previously by P. Stocks and J. M. Campbell.[7]

That the air over Britain is particularly badly polluted can be judged from the fact that the concentration of smoke in Copenhagen is no worse than that found in a small English town.[8] In large industrial towns such as Sheffield the pollution is between five and ten times worse. It seems probable that some of the excess mortality from bronchitis in Britain as compared with Denmark may be due to air pollution, but international comparisons are notoriously difficult, as O. W. Christensen and C. H. Wood[9] have found.

Percy Stocks[10] has recently studied the effects of air pollution on mortality from bronchitis and cancer of the

[1] Registrar General, Sixteenth Report, 1856. H.M.S.O., London.
[2] Ministry of Health. Reports on Public Health and Medical Subjects, No. 95, 1954, H.M.S.O., London.
[3] Wilkins, E. T., *J. roy. san. Inst.*, 1954, **74**, 1.
[4] Reid, D. D., *Proc. roy. Soc. Med.*, 1956, **49**, 767.
[5] Gore, A. T., and Shaddick, C. W., *Brit. J. prev. soc. Med.*, 1958, **12**, 104.
[6] Fairbairn, A. S., and Reid, D. D., ibid., 1958, **12**, 94.
[7] Stocks, P., and Campbell, J. M., *Brit. med. J.*, 1955, **2**, 923.
[8] Campbell, J. M., and Clemmesen, J., *Dan. med. Bull.*, 1956, **3**, 205.
[9] Christensen, O. W., and Wood, C. H., *Brit. med. J.*, 1958, **1**, 620.
[10] Stocks, P., ibid., 1959, **1**, 74.

lung and cancer of the stomach, breast, and intestine. Like other workers, he found that bronchitis was a common cause of death in areas where smoke pollution was severe. Lung cancer also was more prevalent where smoke pollution was high, though further research is needed into the possible role of chimney smoke in the aetiology of this disease. Hitherto there has been no suggestion that atmospheric pollution may play a part in the aetiology of cancer of the stomach, but Stocks has now shown that mortality from the disease is higher than the average in places where smoke pollution is bad. He suggests that this statistical relationship may be the result of town-dwellers eating food which has been offered for sale unwrapped and on which pollutants of the urban air have fallen. Though this is only a suggestion, it should be enough to stimulate vigorous action against unhygienic practices in the display and sale of food.

FELLOWS OF THE ROYAL SOCIETY

Among the 25 new Fellows of the Royal Society elected last week are several whose work has helped to advance medicine, though the list includes no members of the medical profession. Two women are among those elected; and a husband and wife are elected together.

Dr. J. F. Tait and his wife, Mrs. S. A. S. Tait, are elected Fellows for their work on adrenocortical hormones. They discovered aldosterone at the Middlesex Hospital, London, in 1952, by chromatographic separation of fractions of the adrenal cortex. The fraction shown to contain aldosterone[1] (or electrocortin, as it was called first) had higher salt-retaining activity than any other known adrenal corticosteroids. Latterly they have worked on the separation of different adrenocortical hormones from different layers of the adrenal cortex. Unfortunately, like some other outstanding research workers, the Taits found difficulty in obtaining adequate facilities in Britain to continue their investigations, with the result that their recent work has been done at the Worcester Foundation, Shrewsbury, Massachusetts.

Professor F. Bergel, now at the Chester Beatty Research Institute, London, has been elected for distinguished work in several distinct fields of biochemistry. Recently he has been engaged on the experimental chemotherapy of cancer, using amino-acids and peptides as carriers of cytotoxic groups. His earlier work was on the chemistry of vitamins B_1 (thiamine), B_2 (riboflavin), and B_6 (pyridoxine), and on lysergic acid and anticholinesterases. Dr. Ann Bishop, a leading protozoologist, is director of a Medical Research Council unit at the Molteno Institute, Cambridge. She has made fundamental contributions to the understanding of drug resistance in chemotherapy by studying malaria parasites in the experimental animal and the response of the parasites to various synthetic antimalarials. Dr. D. W. W. Henderson, who is director of the Microbiological Research Establishment at Porton, has carried out a long series of investigations into the transmission among experimental animals of micro-organisms causing various respiratory diseases, in particular anthrax and plague. These studies have yielded important results relating size of infecting particle or cloud of particles to the spread of infection. A son of Sir Geoffrey Keynes, the well-known surgeon, is also among the new Fellows—namely, Dr. R. D. Keynes, a Cambridge physiologist. His researches, like those which have brought renown to other members of that school, have been concerned with the transmission of nervous impulses, including investigations into the discharge in electric fish. Among the other biologists elected F.R.S. are two who are unravelling the secrets of protein molecules, and especially the molecular structure of deoxyribonucleic acid (D.N.A.). They are Dr. F. H. C. Crick, at the Cavendish Laboratory, Cambridge, and Dr. M. H. F. Wilkins, at King's College, London. Both are members of Medical Research Council units.

[1] Tait, J. F., Simpson, S. A., and Grundy, H. M., *Lancet*, 1952, 1, 122.

OSSIFYING BRONCHIAL ADENOMA

Spicules of bone would not seem to be so much out of place in tumours of mesenchymal origin, but, to say the least of it, ossification is unexpected in an epithelial tumour; and yet it is by no means rare. It has been reported in both benign and malignant tumours of epithelial origin in many different sites. The presence of bone within bronchial adenomas has recently been reported by Sir Clement Price Thomas and A. D. Morgan.[1] In a series of 63 cases of bronchial adenoma treated by resection they found three cases with widespread ossification. The pictures which accompany this article show islands of mature bone within the stroma of the tumours and also extension of the process of ossification within the adjoining bronchial cartilage.

The explanation generally offered for the phenomenon of ossification in an epithelial tumour is that it is the result of metaplasia in the stroma of the growth, and the fact that in some ossifying tumours bone has been subsequently found in local recurrences and distant metastases indicates that the bone-forming properties are peculiar to the tumour rather than to its environment. To explain the formation of bone in bronchial adenomas Price Thomas and Morgan recall experiments in which transplants of cartilage in soft tissues were followed by death of the cartilage and liberation of calcium in the vicinity, stimulating the connective-tissue cells of the host to form bone. They found that at the periphery of a bronchial adenoma the cartilage may undergo necrosis and calcification and thus afford a medium for ossification.

Tissue necrosis is a well-known factor in the heterotopic formation of bone by old haematomas, laparotomy scars, and degenerate arteries, but necrosis is so universal in tumours that it can be regarded as a factor in ossification only when the tumour is of a slow-growing variety. Bronchial adenomas are slow in growth, and this fact would seem to bring them into line with what is known about ossification in tumours of other organs.

[1] Thomas, C. P., and Morgan, A. D., *Thorax*, 1958, 13, 286.

Clinicopathological Conference

A CASE OF SUBACUTE BACTERIAL ENDOCARDITIS

DEMONSTRATED AT THE

POSTGRADUATE MEDICAL SCHOOL OF LONDON

This is the case of a woman with rheumatic heart disease, complicated by subacute bacterial endocarditis, mycotic cerebral aneurysms, and focal embolic nephritis that did not respond to treatment (Case No. 134,928; P.M. No. 8,410).

Clinical History

Professor T. RUSSELL FRASER: This patient, a 54-year-old clerk, was admitted to Hammersmith Hospital in March, 1958, complaining of vomiting for one day. She had been well until six months before admission, when she had an attack of "right lower lobe pneumonia" shortly after a dental extraction. Since then there had been a gradual loss of weight (one stone—6.4 kg.), increasing irritability and nervousness, with persistent cough and sputum but no haemoptysis. For five weeks there had been occasional aching pains in the limbs, increasing dyspnoea, sweating, and attacks of palpitations. On the night before admission she awoke dizzy and sweating and vomited her tea on rising in the morning. Her past history included rheumatic fever at the age of 18, and thyrotoxicosis at the age of 49, which had been treated with radioactive iodine.

On examination she was pale but well nourished: there was a moist cough, and the temperature ranged from 99 to 100° F. (37.2–37.8° C.) during the first few days. The pulse was 58, with auricular fibrillation, and the blood pressure 145/70 mm. Hg. The jugular venous pressure was raised just above normal, but there was no oedema. Slight finger clubbing but no splinter haemorrhages were present. The apex beat was in the sixth interspace in the anterior axillary line. On auscultation there was a loud first sound with soft systolic and mid-diastolic murmurs in the mitral area and a soft aortic diastolic along the left sternal edge. The pulmonary second sound was loud. There were many crepitations at both lung bases and an area of bronchial breathing at the base of the left lower lobe.

INVESTIGATIONS

Blood. — Haemoglobin 7.1 g./100 ml. (48%); W.B.C. 13,000 (85% polymorphs); erythrocyte sedimentation rate 96 mm./hour.

Chest Radiograph.—The left and right ventricles and right atrium were moderately enlarged. There were small effusions at the bases of both the lungs.

Urine.—No albumin or red cells.

SUBSEQUENT COURSE

She was treated with digitalis, mersalyl, and sulphonamides, but nausea and dizziness continued. At the end of a week haemorrhages appeared in the fundi, red cells were found in the urine, and the spleen was felt. Blood cultures were positive for *Streptococcus viridans*. Penicillin, 2 mega units 8-hourly and streptomycin, 0.5 g. twice daily, were started. The fever continued, with anorexia and dizziness, and on this account the penicillin dosage was doubled, with a favourable response. A week later she relapsed, with a rising blood urea (142 mg./100 ml.) and a fall in the white blood cell count to 1,000, of which 10% were polymorphs. The penicillin and streptomycin treatment was replaced with erythromycin and tetracycline and she was transfused with two pints (1.1 l.) of blood. Two weeks later, after complaining of severe headache for a few hours, she suddenly collapsed into a deep coma with small pupils, conjugate deviation to the left, flaccid limbs, and an extensor plantar response but without other localizing signs. She died two days later without recovering consciousness.

Clinical Diagnosis

(1) Chronic rheumatic heart disease: mitral stenosis and aortic incompetence.

(2) Subacute bacterial endocarditis.

(3) Cerebral haemorrhage (? pontine, ? mycotic aneurysm).

Post-mortem Findings

Dr. I. DONIACH: The body was that of a woman of height 5 ft. 6 in. (1.67 m.) and weight 7 st. 6 lb. (47 kg.). The post-mortem examination was made by Dr. E. D. Williams.

The *brain* weighed 1,460 g. and showed gross enlargement, flattened gyri, and a pronounced cerebellar pressure cone. Coronal sections revealed distension of all ventricles with blood, including the fourth ventricle, though the subarachnoid space of the basal cisterns and the surface of the brain were free of blood. The source of haemorrhage was a small ruptured aneurysm (Fig. 1), 8 mm. in diameter, on a branch of the posterior cerebral artery lying deep in a sulcus on the infero-medial surface of the left occipital lobe. Histological section of the aneurysm showed a ruptured artery, patchy acute necrosis of its wall, and ante-mortem thrombus in the lumen.

The *heart*, weighing 500 g., was enlarged by dilatation of the left auricle, slight hypertrophy of the left ventricle, and moderate hypertrophy and dilatation of the right ventricle. Fusion and rigidity of the mitral cusps had converted the mitral orifice into a crescentic slit 2.5 cm. long, the margins of which were distorted by numerous fibrous vegetations up to 5 mm. in longest diameter. The chordae tendineae were shortened and thickened. The aortic cusps were minimally scarred and presented two small tongue-like vegetations on their contact margins. Histological examination of the heart showed old rheumatic scarring of the myocardium and mitral cusps, healed mitral vegetations, and scattered lymphocytes and histiocytes throughout the myocardium of both auricles and ventricles.

The *lungs* (right 810 g., left 520 g.) showed widespread centrilobular emphysema and diffuse acute albuminous oedema. The pulmonary arterioles appeared normal.

The *kidneys* (right 185 g., left 193 g.) showed a smooth surface, normal architecture, and a fine cortical mottling. Histological examination revealed an advanced focal embolic glomerulonephritis (Fig. 2) affecting 50% of the glomeruli, many of which were almost totally fibrosed.

FIG. 1.—Infero-medial aspect of left occipital lobe of brain showing a ruptured aneurysm of a branch of the posterior cerebral artery and, above it, distension of the sulcus with massive blood clot.

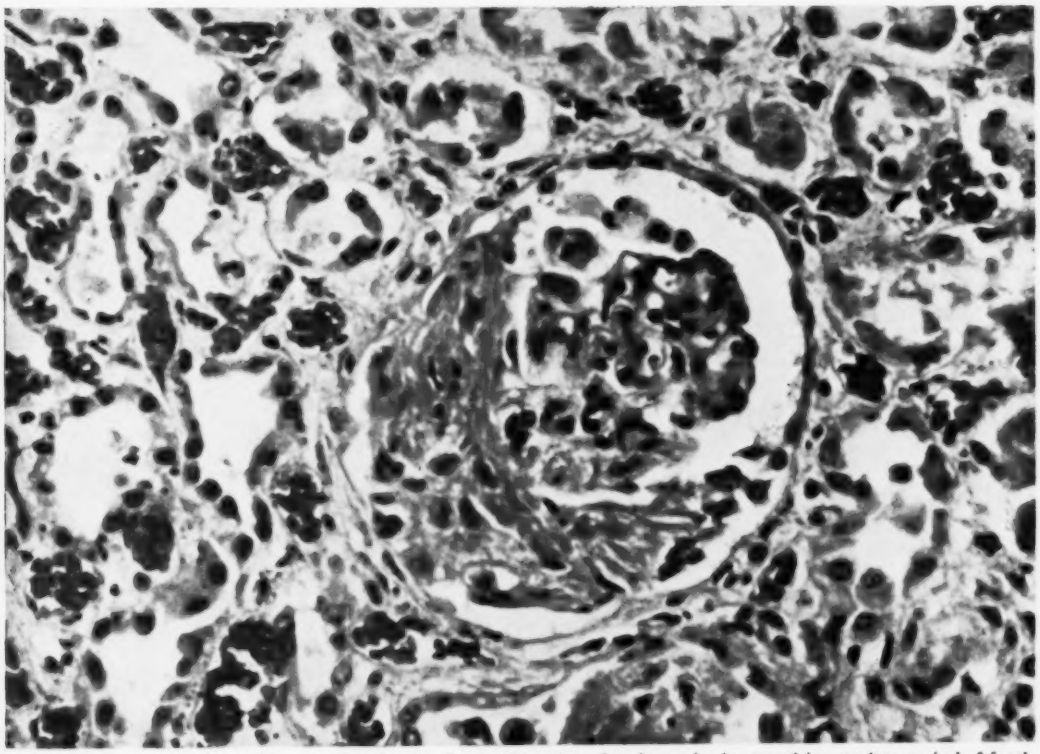

FIG. 2.—Photomicrograph of kidney (×437) showing focal obliteration of a glomerulus by organizing exudate, typical of focal glomerulonephritis.

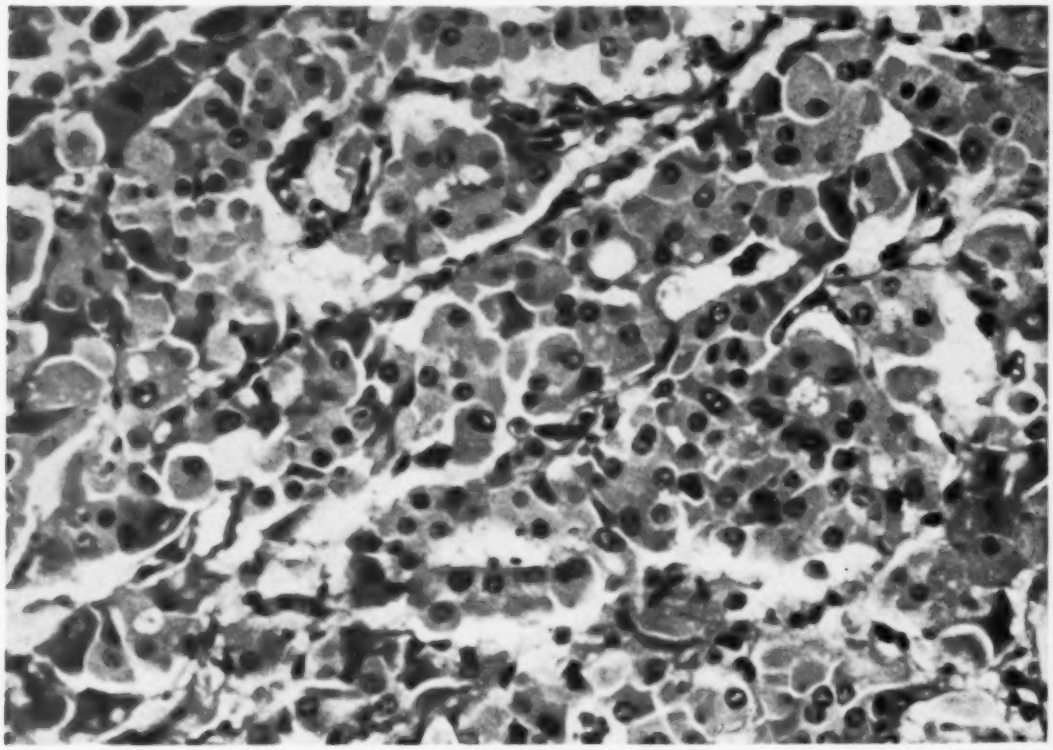

FIG. 3.—Photomicrograph of a Hürthle-cell adenoma of thyroid (×437) showing large polygonal cells, with a finely granular cytoplasm, arranged in solid alveoli and occasional acini.

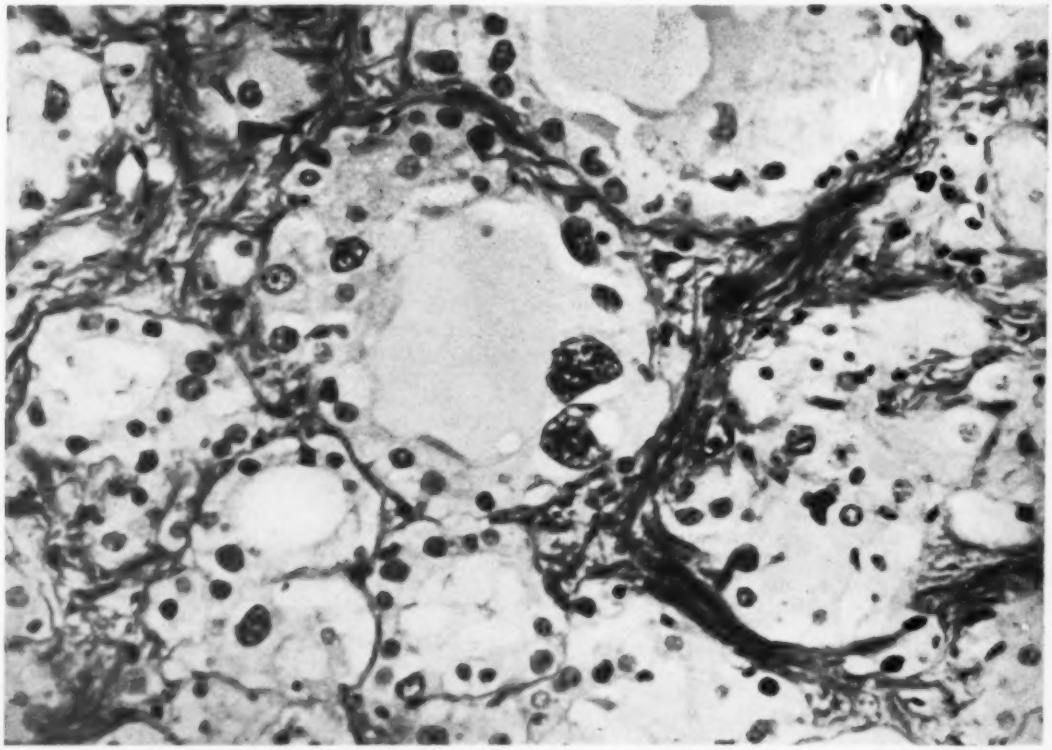

FIG. 5.—Photomicrograph of thyroid (×437) showing acini containing "watery colloid" lined by large cuboidal cells some of which contain giant bizarre nuclei as a result of previous irradiation.

The *liver* (1,685 g.) was congested. The upper alimentary tract was normal, but the mucosa of the *large intestine* showed numerous polyps, largest and most abundant in the caecum. There were two infarcts in the *spleen* (265 g.), one 3.5 cm., the other 1 cm., in diameter. The malpighian follicles were hypertrophied.

The *thyroid* (10 g.) was shrunken and contained a Hürthle cell adenoma (Fig. 3), 2.5×1.5×1 cm., in the lower pole of the right lobe. The thyroid tissue was made up of groups of small follicles separated by interlacing, thick, poorly cellular fibrous bands. The follicles contained colloid and were lined by cuboidal cells with bizarre-shaped nuclei as seen typically after ^{131}I therapy (Fig. 4). The *pituitary* and *adrenals* appeared normal.

Pathologist's Diagnosis

(1) Mitral stenosis.

(2) Healed subacute bacterial endocarditis.

(3) Splenic infarcts.

(4) Focal embolic glomerulonephritis.

(5) Ruptured cerebral mycotic aneurysm.

(6) Irradiated thyroid gland.

(7) Polyposis of large bowel.

Discussion

Professor J. MCMICHAEL: What was the weight of her heart?

Dr. DONIACH: Just over 500 g.

Professor MCMICHAEL: Was the weight increase mainly due to the right or left ventricle?

Dr. DONIACH: The right ventricle was definitely hypertrophied; the left was slightly hypertrophied—its thickness was 1.6 cm. I should say both were hypertrophied, the left slightly less than the right. The lung showed oedema with a histological picture suggesting the oedema was very recent—an acute filling of the lungs with fluid.

Dr. C. PALLIS: The absence of subarachnoid blood is very interesting. This woman didn't have a lumbar puncture after she had lapsed into coma, which was perhaps a very good thing for two reasons. First of all, if we had done a lumbar puncture we would almost certainly have precipitated her death by a few hours in view of the pressure cone that was probably already present; and, secondly, if we had done a lumbar puncture we might have found no blood and that would have led us into even further diagnostic difficulties. When a very rapid rise of pressure of the cerebral contents occurs from a haemorrhage can a pressure cone develop so rapidly that it prevents the egress of blood from the ventricles? This might have been the reason why the blood, although filling the ventricles, didn't get access to the subarachnoid space.

Dr. J. P. SHILLINGFORD: It is often said that subacute bacterial endocarditis is rare in the presence of auricular fibrillation. But this patient had auricular fibrillation and a florid subacute bacterial endocarditis. The second thing which interests me is the slow pulse even in the presence of bacterial endocarditis and cardiac failure.

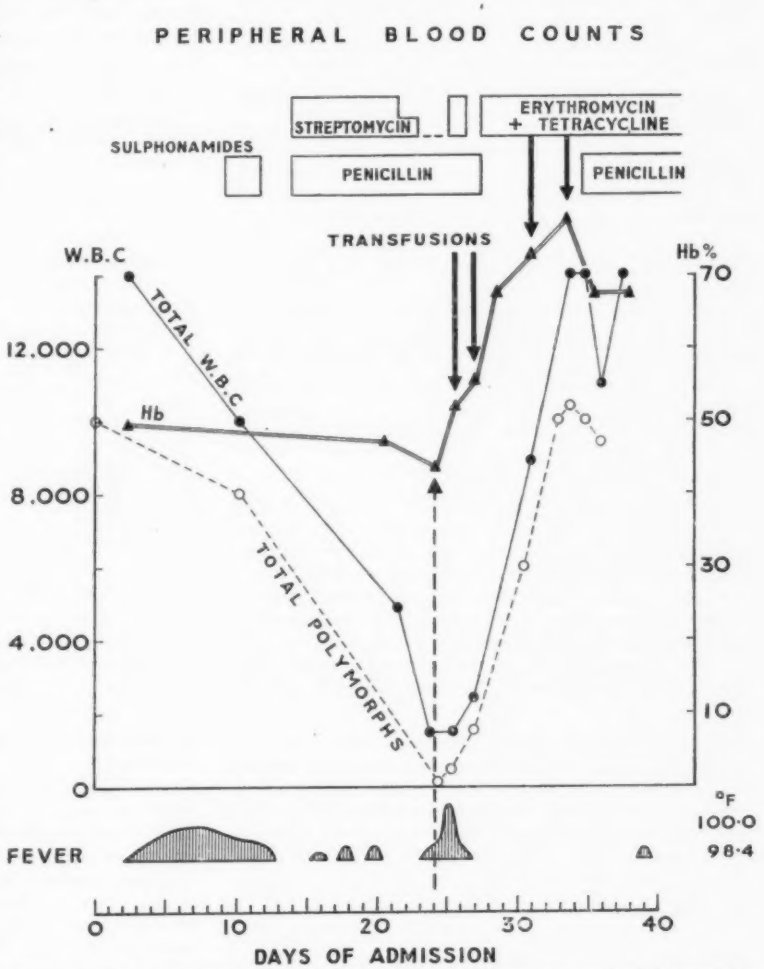

Chart showing relationship of polymorph and total leucocyte counts (and haemoglobin level) to drug treatment.

Professor RUSSELL FRASER: She was on digitalis.

Dr. SHILLINGFORD: Was her pulse slow all the way through the illness?

Professor RUSSELL FRASER: The pulse went up to 120 when she got her febrile, agranulocytosis episode. It went up and it came down later. Most of the time she was in hospital it was reported to have been around 70.

Professor MCMICHAEL: I think the rarity of infective endocarditis with fibrillation is really an expression of the natural history of the two disorders. Once a patient has got diseased valves as a result of rheumatic fever then he is liable to infective endocarditis at any time

in his life, whereas auricular fibrillation is a relatively late development. The chances of infective endocarditis and fibrillation coinciding are very much less than the chance of this happening in sinus rhythm. I think that is the reason. Did you suggest that penicillin might have caused the agranulocytosis? I did not know that this was a complication of penicillin.

Professor RUSSELL FRASER: I am afraid we can't say for certain what it was due to, but there is good evidence that it wasn't the penicillin. She was put back on to the penicillin on May 5 (see Chart) and remained on it some days without any disadvantage. We thought it must be due to the streptomycin, by inference.

Professor MCMICHAEL: Is that a recognized complication?

Professor RUSSELL FRASER: Well recognized, but certainly a rare complication all right. Unfortunately we have had occasion recently to deal with an aplastic anaemia due to streptomycin, so perhaps it seems more common to us than it really is. With regard to her heart output, when I was just looking back over the old notes, I noticed that when we saw her in 1952 for her thyrotoxicosis she did not have auricular fibrillation: and that is another little point. Cardiologists are always telling us that, if an elderly woman develops heart failure, it is unlikely to be due to thyrotoxicosis unless she has got fibrillation.

THE RUPTURED ANEURYSM

Dr. PALLIS: May I ask Dr. Doniach whether arteries of the calibre of the posterior cerebrals are supplied with vasa vasorum? If they are, might not the type of focal destruction of the arterial wall we have seen in this case be due to occlusion of these minute vessels? In the kidneys there was evidence of embolism so discrete that at times it picked out a solitary glomerulus in a whole field. Could there have been a similar state of affairs in the wall of the affected posterior cerebral artery?

Professor MCMICHAEL: Sometimes one gets these aneurysms in infective endocarditis in quite big arteries. We have seen it in the femoral, the main renal artery, and so on. However, it's difficult to imagine a small infective embolus sitting on a single spot in the wall of a vessel the size of your little finger, isn't it?

Professor RUSSELL FRASER: I don't know whether Dr. Doniach would like to comment on whether the site of this haemorrhage was a likely one for a mycotic aneurysm. Could the aneurysm have been the cause of her persistent earlier troubles—the vomiting and dizziness?

Dr. DONIACH: I think we shall have to put the question to Dr. Pallis, but I can tell him that the aneurysm lay deep in the calcarine fissure.

Dr. PALLIS: That makes it awkward to account for the dizziness.

Dr. DONIACH: I should like to ask Professor Russell Fraser, what is the present attitude towards dental extraction in a patient with mitral disease? Do you always cover the extraction with penicillin? This was a classical case, wasn't it? She had five dental extractions and she developed subacute bacterial endocarditis.

Professor RUSSELL FRASER: Penicillin should be the routine treatment in these cases.

RADIO-IODINE THERAPY

Professor MCMICHAEL: Would you like to say something about the pathological changes in a thyroid treated by radio-iodine, Dr. Doniach?

Dr. DONIACH: Yes. These have now been recorded in a fair number of cases. The picture we have seen to-day fits all the pathological descriptions, and I think it is associated with a pretty normal clinical picture.

Professor MCMICHAEL: You think that these odd-looking cells (Fig. 4) are in fact functioning so far as thyroid secretion goes. Were they all like that?

Dr. DONIACH: Not all, but most of the thyroid seemed to show this anomaly.

Professor MCMICHAEL: Do you still take the view that radio-iodine suppression of thyroid function should be reserved for people well past middle life in view of the dangers of thyroid carcinoma later on? These were nasty-looking cells.

Dr. DONIACH: Well, the fact remains that no cases of carcinoma have developed in thyroids so treated, and many thousands of patients have had radio-iodine since about 1946 or 1947. I think myself that there are two stages in this carcinogenesis—the initiating stage which these bizarre cells reflect, and then there is a stage at which the cells if stimulated to proliferate might produce cancer. I think that if such a patient were submitted, say, to a course of thiouracil, a long course which would make the cells grow, or if such a patient moved to a goitrogenic district, he would run the risk of cancer. If they are not submitted to that, I think they are free from danger.

Professor MCMICHAEL: Do you think the period of 12 years is a long enough follow-up? Some people get carcinoma as long as 20 years after radiation of the skin.

Dr. DONIACH: Yes, you are quite right.

Professor MCMICHAEL: Another eight years. Meantime caution is the watchword, is it?

Professor RUSSELL FRASER: It is certainly still our practice here to give the treatment only to the people over the age of 45, and that is the practice in a lot of places. There are two reasons for that: first, there are other treatments which are really pretty satisfactory for the younger people; and second, there is no good reason to rush into any treatment which might have a hazard. I suspect that the extent of the hazard is really fairly slight, however. But there is no doubt whatsoever that irradiation of the thyroid region in young children has been shown to be productive later of carcinomas; but of course the very young are more liable to get carcinoma after irradiation than are elderly people. This has been particularly well shown in those who have had radiation for an enlarged thymus in infancy.

With regard to this patient's chest history, we went into that very carefully when she came in on this last occasion, because at first we thought that her fever could be attributed to her six months' bronchitis, which is what the history sounded very like. Her earlier history did not show any unusual liability to coughs and respiratory infections. She had had no severe pneumonias or anything unusual for a woman in her early fifties. She had been relatively free from chest disability. In fact, when she came in 1952 for an illness which led to the diagnosis of thyrotoxicosis, one of the odd features was her relative freedom from effort dyspnoea.

Dr. B. E. HEARD: There is a remote possibility that the pathological changes in her lungs could be the result of a respiratory infection during childhood.

Professor RUSSELL FRASER: She did, I feel sure, have a respiratory infection for some long time during the months preceding her admission.

Dr. HEARD: That is a more likely explanation.

We are grateful to Dr. J. P. Shillingford and Dr. B. E. Heard for assistance in preparing this report and to Mr. W. H. Brackenbury for the photographs.

FIRST CATHERINE CHISHOLM MEMORIAL LECTURE

PROFESSOR WALLGREN'S SURVEY OF PAEDIATRICS

Dr. Catherine Chisholm, the distinguished Mancunian paediatrician who founded the Duchess of York Hospital for Babies, died in 1952. Six years later Professor Arvid Wallgren, of Stockholm, delivered the first Catherine Chisholm memorial lecture at Manchester.* It was entitled "A Lifetime of Paediatrics."

When Catherine Chisholm started upon her career as a physician 50 years ago, said Professor Wallgren, little was being done to improve the living conditions and the state of health of children. The situation at that time corresponded fairly closely to that now characteristic of many Asian countries. At the beginning of the century there was little difference in this respect between the various countries in Europe, and he would therefore illustrate his description of the rise of child care by referring to Sweden, which he knew best. Progress in child health had run a similar course in England. During his particularly wide survey, Professor Wallgren discussed many topics of interest to paediatricians. A summary of his remarks on congenital abnormalities and B.C.G. is given below.

Congenital Malformations

During the last decade, said Professor Wallgren, new knowledge had been acquired about the relationship between ill-health in pregnancy and malformations of the infant. In 1941 Gregg, in Australia, made the now well-known observation that one of the mildest of acute specific infections in children, rubella, when it occurred in a woman during the first two to three months of pregnancy, could produce malformations in her offspring. This observation had since been confirmed in numerous countries. In Sweden, Lundstrom had made a thorough study of the influence of a great epidemic of rubella. He found that rubella in the first few months of pregnancy not only produced malformations but also increased the incidence of stillbirths, abortions, and premature births.

This was an indication of *one* possible cause of hitherto unexplained malformations in the newborn and of stillbirths. What the mild rubella could do, probably other infections might also do. Already there had been reported a certain number of cases in which other specific maternal infections, viral or bacterial, had apparently given rise to disturbances in foetal development. It seemed as if these malformations depended more on the time of invasion by the noxious agent than on its type.

From experimental research and clinical experience it had been learned that radiation might produce such foetal disturbances. A long time ago it was recognized that radiological examination of the abdomen at the beginning of pregnancy might cause microcephaly. Nowadays this did not happen, because the risk of this procedure was well known. But still, microcephaly did occur. There were certainly many other sources of radiation, especially during the last decade with its rather indiscriminate use of atomic energy for various purposes.

Little was known about the influence of many possibly relevant factors—for instance, how stress, physical exhaustion, or drugs taken by the mother might produce disturbances in the delicate mechanisms of embryogenesis. Deficient nutrition of the pregnant animal had been shown to produce various kinds of disturbances in the offspring. There was reason to believe that the same might be true also in human beings. The mechanism of foetal development was very delicate and complicated, and was influenced easily by many external agents that had a powerful effect upon the mother, and it might therefore seem surprising that malformations and foetal illnesses did not occur more often.

B.C.G. Vaccination

England and Sweden were moving in opposite directions so far as B.C.G. vaccination was concerned. While B.C.G. in Sweden thirty years ago was introduced as a part of a country-wide anti-tuberculosis campaign and developed gradually, finally leading to almost 100% vaccination of infants, it was only during the last decade that B.C.G. was tried tentatively at some centres in England, especially in Manchester by Professor Wilfrid Gaisford. "Perhaps," said Professor Wallgren, "it was the keen interest of Dr. Catherine Chisholm in B.C.G. vaccination that inaugurated this measure in your city." Early in the history of B.C.G. inoculation she endeavoured to start an experimental study of its efficiency. To her disappointment the project was turned down.

In leading circles in England, Professor Wallgren thought, there was still scepticism about the value of B.C.G. If England was late in introducing B.C.G. it had at least afforded the best proof of the efficiency of the vaccine by the remarkable results reported by the Medical Research Council. The tuberculosis research unit of the Medical Research Council succeeded by careful planning in avoiding all the pitfalls and statistical errors that made almost all previous follow-up studies subject to criticism. Catherine Chisholm lived to see B.C.G. adopted as an efficient prophylactic in the United Kingdom.

The interest in B.C.G. vaccination had since begun to diminish in Sweden, and there were some authorities who questioned if it was still necessary to use mass B.C.G. vaccination in a country where the tuberculosis morbidity and mortality rates in children had decreased so remarkably. It was very rare indeed to-day to see tuberculosis in infants and small children, and at school age only a few per cent. of unvaccinated children were tuberculin-positive. At the same time the advent of new specific chemotherapy had provided a very effective way of preventing the development of serious complications in infected children.

There were in Sweden at present practically no children dying from tuberculosis, thanks to a well-organized medico-social anti-tuberculosis campaign, B.C.G. vaccination, and appropriate use of chemotherapy and surgery. The progress during the last 50 years had been almost unbelievable.

Paediatrics, Professor Wallgren concluded, was concerned with the whole child, his mental as well as his physical development and his adjustment to his environment in the home, at school, and in society. Paediatricians, perhaps more than any other doctors, had emphasized the importance of social and emotional factors not only in the aetiology and treatment of disease but also in the day-to-day process of living.

*The lecture was given on June 30, 1958.

Drug Treatment of Disease

ADDICTION TO DRUGS: PART I

BY

MAURICE PARTRIDGE, D.M., D.P.M.

Consultant Psychiatrist, St. George's Hospital, London

While the problem of addiction has never been large in Great Britain there has been always within living memory a core of addicts to alcohol, to morphine and its derivatives, to cocaine, and, in very small numbers, to chloral and paraldehyde.

It is to be expected that newly introduced drugs may give rise to new addictions, but the number that actually do so seems to be small. Yet some new addictions have developed over the last twenty-five years. Thus, addiction to the barbiturates has made its appearance since, thirty years after their original introduction, they achieved therapeutic popularity in the 1930's. In 1935 came the first clinical application of amphetamine (for narcolepsy), and, as its stimulating properties became known to a wider public, abuse and addiction were found to occur. Subsequently, the hopes that the newer morphine derivatives, dihydromorphinone ("dilaudid") and levorphanol ("dromoran") were non-addictive were found not to be based on fact. When pethidine (a piperidine derivative) came to be widely used as an alternative, pethidine addiction followed. Likewise, when the synthetic analgesics methadone ("physeptone") and phenadoxone ("heptalgin") were developed, these too were found to be addictive. More recently addiction has been noted, though to no important extent, to methylpentynol ("oblivon") and to carbromal with bromvaletone ("persomnia"); the former could at first be obtained without prescription, the latter is still thus obtainable.

Of these new addictions, that to pethidine is the most dangerous in that it tends to be severe, but methadone, phenadoxone, dihydromorphinone, and levorphanol are also drugs that have their dangers. Addiction to barbiturates is no doubt commoner, but is remarkably rare in Britain considering the prodigal amounts that are prescribed. Such addicts often combine it, as do those addicted to morphine and its derivatives, with amphetamine addiction, one substance being used to offset the effects of the other, though amphetamine addiction can also occur alone. Methylpentynol and carbromal with bromvaletone are usually taken by addicts as adjuvants to more powerful substances, or as being better than nothing when other supplies have failed.

Nature of Addiction

Addiction may be said to be established when the drug has become a necessity to the patient. He cannot do without it because he cannot tolerate the symptoms that occur in its absence. An example is the established alcoholic who needs a morning dose to offset the shakiness and anxiety that have arisen from the previous day's excesses. He has become physiologically dependdent on the addictive substance for his well-being—more accurately for his well-feeling—and the extent of the dependence will vary according to (1) the severity of the symptoms that result from abstinence, and (2) the extent to which the particular personality can tolerate them. Patients with a low tolerance of discomforts and frustrations are those more likely to be addicts, just as they are those more likely to turn to drugs in the first place. The development of addiction, in fact, depends much on the personality. The form of the addiction depends more on circumstances and opportunity. The symptoms will depend on what type of addiction has resulted from the circumstances and opportunities with which the particular personality has been confronted. Little is known of the precise manner in which physiological dependence comes about, but it certainly seems to occur, and that it does so is an indication that the problem of addiction involves far more complicated factors than simple weakness of the will.

Symptoms of Addiction

These will vary to some extent with the substances involved. When, as often happens, the patient does not disclose the facts, a clue to the existence of addiction may be afforded by complaints of otherwise inexplicable oscillations of mood coupled with inefficiency in performance, impairment of grasp which may or may not be transient, and periodic "islands" of amnesia with more or less forgetfulness between. These are suggestive of a varying level of intoxication. Thus, a moody employee who gets through less work, deals with it incompletely, and fails to remember on Thursday a person whom he had interviewed and about whom he had made notes on the previous Tuesday, has probably been carrying on under the influence of alcohol or drugs in excessive quantities. There are other possible explanations, but this one should come to mind. The same is true of confusional episodes, especially when an otherwise healthy patient gives a history suggestive of nocturnal delirium. Apart from such general effects of intoxication, there may be specific symptoms.

Addiction to Morphine and its Derivatives.—The appearance of the patient, languid, sallow, undernourished, with loss of hair and brittle nails, may be suggestive. Pin-point pupils and injection marks should be looked for. The mental symptoms are not prominent, and amount to no more than laziness, lack of persistence, day-dreaming, and increasing unscrupulousness. Withdrawal symptoms are very marked. Mentally, these consist of depression, irritability, anxiety with restlessness, and profound malaise. Physically, characteristic symptoms are yawning, irritation in the nose with sniffing and sneezing, salivation, and lacrimation; shivering, tremor, and twitching; variable pains and in particular muscular cramps; and alimentary disturbance in the form of nausea, vomiting, and diarrhoea. The withdrawal syndrome may be distressingly severe. The gradual development of an irritable, restless malaise, followed by sudden cheerful contentment after a brief absence, may suggest addiction when the patient is trying to conceal it.

Addiction to heroin (diacetylmorphine) gives rise to a similar clinical picture, as does addiction to the morphine derivatives levorphanol and dihydromorphinone.

Addiction to Methadone and Phenadoxone.—These synthetic analgesics may be considered here because the effects of addiction to them are in general similar to those caused by addiction to morphine and its derivatives, despite the differences in chemical structure. The withdrawal symptoms, however, tend to be less severe.

Addiction to Cocaine.—The mental symptoms are more prominent. The main effects of the drug are elation and activity, but its continued use leads to marked mental changes. The principal one is the development of hallucinations. These are usually tactile and auditory. Tactile hallucinations as of small animals crawling underneath the skin are a special feature of this addiction, though not invariably present. The auditory hallucinations are more important because they are usually frightening to the patient, lead to various misinterpretations, as in chloral addiction (see below), and so may encourage aggressive retaliation or unpredictable violence. Although such developments tend to be worse at night, the patient may continue hallucinated and misinterpreting for long periods though able to appear more or less normal outwardly, apart from a moody restlessness with an anxious irritability. Acute delirium may supervene later. Physically, pallor and malnutrition are usual, as are injection marks or ulcerations of the nasal mucosa, according to the routes by which the drug is usually taken. Withdrawal symptoms are mild and consist mainly of insomnia, general malaise, and palpitation.

Addiction to Chloral.—Again the mental symptoms are prominent. Apart from moodiness and that slow, muddled state of forgetful inefficiency that we might call fuddledness, the chloral addict also tends to develop auditory hallucinations which form the basis for suspicious misinterpretations, as when D. G. Rossetti believed a cabman to have placed a bell on the roof of the cab to annoy him, and Gilbert Pinfold believed himself to be the centre of a political plot owing to his having heard many complicated pronouncements that were inaudible to other people. The withdrawal symptoms do not seem to be specific or severe. As to *paraldehyde addiction*, there are no special features, and the clinical picture of *alcohol addiction* is too well known to need repetition.

The foregoing, with the addition of the newer morphine derivatives and the synthetic analgesics, are the classical addictions with which doctors have long been more or less familiar. It remains to consider the more modern addictions to pethidine, to the barbiturates, and to amphetamine.

Addiction to Pethidine.—This is the most dangerous of the newer addictions, both because the addiction itself is a severe one and because it carries a considerable mortality. The drug is usually taken in the first place for its analgesic and antispasmodic properties, and if this is long continued the patient experiences withdrawal symptoms of sweating, malaise with anxiety and depression, and a general feeling of heaviness, especially in the limbs, which may also be affected by cramp-like pains. Further and larger doses may then be required to allay these symptoms. With larger doses a confusional state with hallucinations, illusions, and secondary misinterpretations may develop. The withdrawal symptoms are then more severe, with the addition of tremors and twitchings, and convulsions have been known to occur, as have choreoathetotic movements.

Addiction to Barbiturates.—The patient develops a chronic state of more or less intoxication. The clinical picture varies according to the extent to which the patient is intoxicated, from a disinhibited over-talkativeness with restlessness, to a slow, forgetful fuddledness with, between whiles, an anxious gloom. Larger doses may lead to actual confusion or subdelirium, with amnesic episodes. Physically, there may be slurred speech, ataxia, nystagmus, and generally impaired co-ordination. Withdrawal symptoms consist mainly of anxiety, with tremors, palpitation, postural dizziness, nausea, and vomiting, but if the dosage has been large, withdrawal fits are not uncommon. Rarely, a delirium may follow withdrawal, with a close resemblance to delirium tremens.

Addiction to Amphetamine.—The substance confers a feeling of confidence combined with energy, and a subjective sensation of mental alertness and agility. When the effects wear off, the habitual user experiences a rather intense lethargy and gloom, which leads to a further and often to a larger dose. The cycle is then repeated. The wakefulness induced by the drug causes some patients to turn night into day, pursuing a flurry of activity through the small hours. With large doses deliria with auditory and visual hallucinations can occur, leading, as with other drugs, to misinterpretations usually involving alarm and apprehensiveness.

(To be concluded)

TRIBUTE TO SIR WILFRID LE GROS CLARK

A bronze portrait bust (here illustrated) of Sir Wilfrid le Gros Clark, F.R.S., the work of Sir Jacob Epstein, was presented last week to the Department of Human Anatomy at the University of Oxford to mark the occasion of Sir Wilfrid's silver jubilee as Dr. Lee's Professor of Anatomy. The portrait bust was commissioned by colleagues, associates, and former pupils of Sir Wilfrid as a tribute to his eminence and leadership in the fields of anatomy and physical anthropology. The presentation was made on the occasion of the opening of the new extensions to the department of human anatomy at Oxford by Sir George Pickering, Regius Professor of Medicine, who said that Sir Wilfrid le Gros Clark had played, and was still playing, a unique part in the revolution that was taking place in the study and teaching of anatomy. The cost of the new department, when completed, is expected to be about £160,000. An impressive feature is the new dissecting-room with its curved roof of heat-resisting glass.

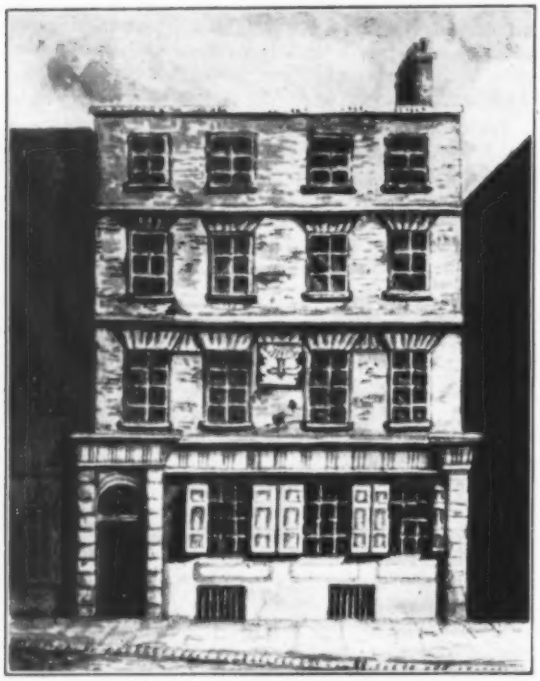

FIG. 1.—Stone House, No. 5, Knightrider Street, rebuilt after the Fire of London about 1670 on the site of the original College house (Linacre's house). Enlarged from Dr. Macmichael's plate in *The Gold-headed Cane*.

HOMES OF THE ROYAL COLLEGE OF PHYSICIANS OF LONDON

The Royal College of Physicians of London is to surrender the lease of its site and building at Pall Mall East in favour of the Government of Canada. The building is to become part of the present Canada House. At the same time the Crown Estate Commissioners will grant the College a lease of the site of Someries House, a Nash house at the south-east corner of Regent's Park, recommended for demolition. It is hoped to start work on a new building on this site in 1961.

The new building is to provide lecture rooms, a large library with reading rooms, a common room for Fellows, committee rooms, and accommodation for the secretarial staff. It will balance the building for the Royal College of Obstetricians and Gynaecologists on the opposite side of the park.

A severe epidemic of sweating sickness in 1518, underlying as it did the medical problems of the time, may have been the deciding factor in Henry VIII's grant to Thomas Linacre of letters patent incorporating a "perpetual Commonalty or Fellowship, of the Faculty of Physic." After its foundation in that year the College met regularly at Linacre's house, 5, Knightrider Street, south of St. Paul's Cathedral. Linacre eventually gave the house to the College, which continued to

FIG. 2.—Amen Corner. No illustration of the second College survives, but this nineteenth-century drawing has been based on a contemporary document in which details of the building are given.

meet there for nearly a century. It was destroyed in the Great Fire of 1666. In 1614 the house had become inadequate for its purpose and a more suitable house at Amen Corner, Paternoster Row, was purchased from the dean and chapter of St. Paul's. The College held its first meeting there on August 23, 1614.

During the plague of 1665 most of the College officers retired to the country for safety, among them Dr. Christopher Merrett, Harveian librarian and custodian of the College. During their absence, according to Munk, "the College was broken into, and the treasure chest, containing the whole of the College funds, now greatly augmented by the contributions of the honorary fellows, was robbed of its whole contents." In the following year the College building and most of its contents were destroyed in the Great Fire. The fire began on the night of September 1–2, but did not reach

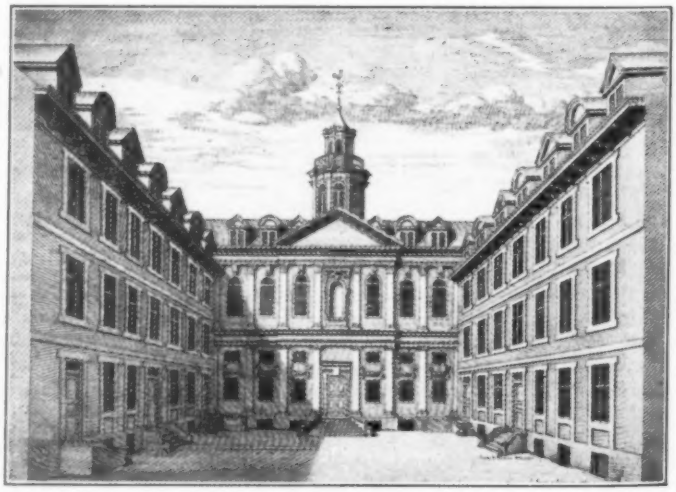

FIG. 3.—Warwick Square.

the College building until the 5th. In the interval Dr. Merrett removed about 100 books and the College records, Harvey's portrait, and insignia to a place of safety.

The Fellows met for the first time after the Fire on October 1, 1666, at the house of Sir John Langham, continuing to use his house for some time afterwards. Plans were at first made to rebuild at Amen Corner, but these were later abandoned in favour of a site at Warwick Lane, where a new building for the College was erected. It was occupied for the first time on February 25, 1674/5. Robert Hooke's diary in the Guildhall Library establishes that it was he and not Wren who was architect for the principal buildings.

In 1674 it was announced that Sir John Cutler, Bt., had offered to build an anatomical theatre in the College at his own expense. This was added to the east side of the existing buildings and formally opened on January 21, 1678/9. The great dome of the Cutlerian theatre was a landmark in the City and thus commemorated by Samuel Garth:

> "There stands a dome majestic to the sight,
> And sumptuous arches bear its awful height;
> A golden globe placed high with artful skill,
> Seems to the distant sight a gilded pill."

By the beginning of the nineteenth century the building at Warwick Lane, while still adequate in size and design, was in a dilapidated condition and in surroundings which had greatly deteriorated since its construction. Population and fashion had moved westward and it was felt that the College should follow. In 1814 permission was obtained for the College to hold its meetings and exercise its powers within the city of Westminster. Mainly through the exertions of Sir Henry Halford, President of the College, a suitable site at Pall Mall East was acquired in 1820. Here the present building, designed by Sir Robert Smirke, was opened with due ceremony by Halford on June 25, 1825. During the last war the College building suffered some damage during an air raid but the books and other treasures were rescued.

The illustrations have been provided through the courtesy of Mr. L. M. Payne, Assistant Librarian of the College.

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Munk, W., *Roll of the Royal College of Physicians of London*, 1878, 2nd ed., Vol. III. London.

FIG. 4.—Pall Mall East.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Live Poliomyelitis Vaccine

SIR,—Certain points raised in Dr. A. B. Sabin's recent paper on live poliovirus vaccines (*Journal*, March 14, p. 663) merit further discussion, and we would like to deal in turn with the four topics to which he and we[1] gave special consideration.

(1) *The neurotropism of virus excreted by vaccinated individuals and their contacts.* — Dr. Sabin draws attention to the variation in results obtained by different workers in tests for neurotropism of polioviruses in monkeys and has discussed the various methods employed. While we agree that a standard technique is desirable, it must be remembered that in an experimental method of this type consistency is most important. The test for monkey neurotropism is a comparative one and there is nothing absolute about it. We have consistently used the technique taught by Bodian *et al.*[2] and have been less troubled by traumatic lesions than Dr. Sabin appears to have been. We agree with him that it is important to inoculate the fluid slowly.

In discussing the finding of Clarke *et al.*[3] in their trial of Sabin's type 3 vaccine virus, Dr. Sabin draws attention to the low bicarbonate content of the cultures they used for isolation of faecal virus. He points out that this medium preferentially selects the more neurotropic virus particles, unlike the medium he uses, which is the optimum for demonstrating avirulent virus. Through the kindness of Professor C. H. Stuart-Harris we were able to test specimens from the volunteer (1203) whose faeces yielded the virus of greatest neurotropism.[3] Unfortunately the original stool specimen was not available and we were provided with first-pass tissue culture fluid. This was given one additional tissue culture passage using a medium similar to that used by Dr. Sabin and then tested intracerebrally in rhesus monkeys. The results are summarized in the table.

Our assessment of the virus excreted by volunteer 1203 on the fourteenth day is that it was still definitely in the "avirulent" range—i.e., it was much less neurotropic than any viruses we have tested which were isolated from the stools of patients with acute poliomyelitis. While it is quite clear, from the manner in which Professor Stuart-Harris and his colleagues conducted their trial, that the introduction of a "wild" virus during the observation period was highly unlikely, we would have the same difficulty in the laboratory determining whether we were dealing with a vaccine virus or a "wild" virus that Dr. Sabin had in a recent trial.[4]

This surely is the crux of the problem. Are vaccine viruses which can spread and have a monkey neurotropism similar to some "wild" avirulent strains going to prove stable in the field under varying

Intracerebral Virulence Test in Monkeys of Virus Excreted by Volunteer 1203[3]

Inoculum Logs	Monkeys Inoculated with Virus Excreted on 2nd Day		Monkeys Inoculated with Virus Excreted on 14th Day			
	Paralytic Rate	Histology* Poliomyelitis Lesions	Paralytic Rate	Histology* Poliomyelitis Lesions	Onset of Paralysis Day	Extent of Paralysis† Grade 5–0 in Limbs
6	0/3	0/3	—	—	—	—
5	0/3	0/3	2/3 (?3/3)	2/3	17 17 ?18	5, 5, 3, 4 5, 5, 4, 4 5, 5, ?4, 5
4	—	—	2/3	3/3	17 19	5, 5, 4, 5 5, 5, 5, 4
3	—	—	0/2	—	—	—
2	—	—	0/2	—	—	—

* Routine blocks of cortex, mid brain, pons cervical and lumbar enlargements.
† Order of scoring—upper right, upper left, lower right, lower left.
The histology was carried out by Dr. Florence McKeown, Department of Pathology, Queen's University, Belfast.

conditions and circumstances? And, if they are stable, how easy will it be to prove this when one considers all the coincidences that might arise during large-scale trials? We believe that Dr. Sabin's vaccine viruses may well have been "changed beyond recall," but we would have liked to see this proved before large-scale trials were initiated. Like him we place great weight on results personally obtained by him, and we were pleased to find reports in his paper on the first few non-immune children he has studied after feeding his current vaccines. We have previously drawn attention to the dangers of assuming that attenuated poliovirus vaccines will behave in the same way in children as in adult volunteers.

We presented some data[1] showing that the stools of a healthy contact yielded less neurotropic virus than those of a paralysed child. Dr. Sabin suggested that this might represent what occurs at the end of an epidemic—that the virus changes to avirulence with continued alimentary passage. This may well be the case, but, just as a virus may lose its neurotropism towards the end of an epidemic, so an increase in viral neurotropism could start an epidemic. The results which we presented were from a paralysed child and contact early in an epidemic year.

(2) *The persistence of antibody and its relation to resistance of the alimentary tract.*—We have difficulty in imagining that alimentary tract resistance after live virus vaccination is necessarily durable when both Professor Stuart-Harris and his colleagues[3] and Dr. Sabin have succeeded in infecting a proportion of naturally immune subjects. Until more data are available about the current strains of vaccine viruses it seems preferable to predict the long-term efficiency of the vaccines on the basis of circulating antibody. Though Dr. Sabin gave results on only a small number of children vaccinated with his present strains, their antibody response was undoubtedly good and of the same order as that following natural infections.

(3) *The effect of multiple doses of Salk vaccine and high levels of antibody produced by killed vaccine on multiplication of poliovirus in the intestine.*—We raised the question of whether "*adequate*" immunization with "*potent*" formalinized vaccine might not so alter the pattern of virus excretion in vaccinated subjects that polioviruses would disappear from a community. Dr. Sabin gives some details of a trial on 25 vaccinated children, and quotes the results obtained as evidence that the use of formalinized vaccine has no effect on virus multiplication in the intestinal tract. As there are no control results, and as the vaccine used for three of the four injections was obviously not potent, we do not feel that this important question is any nearer being solved. Even with *inadequate* immunization, Dr. Sabin found that multiplication of virus in the pharynx was inhibited. We cannot agree with him that pharyngeal virus is necessarily of no epidemiological importance. Lower titres of virus are generally found in the pharyngeal secretions than in the faeces, but virus can and does find its way into the saliva in small amounts (it is important to remember that we measure tissue culture infective doses in the laboratory and not human infective doses, which may very well be higher). We agree with Dr. Sabin that most of "the pharyngeal poliovirus is swept down into the stomach," but, after all, in many households most of the faecal virus is swept down the lavatories.

In general children have much greater opportunities of consuming each other's saliva than each other's faeces, and the oral–oral spread of virus is simpler and more direct than faecal–oral spread. We are hesitant, therefore, to dismiss oropharyngeal virus summarily as being of no epidemiological importance.

(4) *The present status of field trials.*—We consider that, at the present time, the known risks of field trials in suitable countries are small, and it is difficult to visualize how they could do more harm than good. But unknown risks do demand some degree of "non-specific caution," and it is interesting to learn from Dr. Sabin that recently over 200,000 people in the Congo were fed with a live poliovirus vaccine contaminated with an unidentified cytopathogenic virus.

In conclusion, may we express hope that the trials of Dr. Sabin's vaccine now being conducted will prove successful in defining limits of safety and effectiveness? We have a great admiration for Dr. Sabin and his work and hope that he will consider any criticisms we have made as fair comment representing a different approach to the interpretation of available data.—We are, etc.,

Belfast. G. W. A. DICK.
D. S. DANE.

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3 Clarke, S. K. R., Goffe, A. P., Stuart-Harris, C. H., and Herzog, E. G., *Brit. med. J.*, 1958, **2**, 1188.
4 Sabin, A. B., *Advanc. Pediat.*, 1958, **10**, 197 (Table V).

"Getting Married"

SIR,—I am sending you some comments on the controversial articles in the recent edition of "Getting Married." I believe they show that Dr. Eustace Chesser, in his contradictory statements, stands condemned out of his own mouth.

"Is chastity outmoded?" Chesser asks, and he answers, "I doubt it. But it cannot be denied that we are moving in that direction." Like Chesterton's Dr. Pellkins, who said, ". . . when we see a pig in a litter larger than the other pigs, we know that by an unalterable law of the Inscrutable it will someday be larger than an elephant . . ." so Dr. Chesser, too, seems to anticipate that this movement will go on unhaltingly as far as ever his imagination can stretch.

"Principles should not be sacrificed to expediency. But are we so sure of the principle?" Chesser asks, and he continues, ". . . without any religious and social

taboos, this question of right and wrong might not arise." Indeed, without religion, the terms of right and wrong have no sense, but in spite of this Chesser continues to speak of things being, or not being, justifiable and about allegiances owed, about morality, about spirituality and integrity. All of the terms are used very vaguely.

". . . to condone human frailty . . . is one thing, to encourage it is quite another," Chesser dogmatizes, but on the same page we find his statement that pre-marital sexual intercourse can be more than ordinarily pleasant. A "statement of fact" he might call it, but it is a fact presented with a bias and an encouragement to go the way of human frailty. Incidentally, what about the "more than ordinarily pleasant" experience of having successfully battled against temptation?

"From our early years, we are made to feel that the pleasures of the body are in themselves evil and sinful," says Chesser. Christians will agree with him that such teaching, where it has been given (this is largely a matter of the past), was certainly wrong. But he continues, "by the kind permission of society, we are allowed to lose our chastity when married. All too often events prove this to be too little and too late." What is Chesser's definition of chastity one wonders; and does his cry of woe "too little and too late" not encourage what he pretends only to condone?

"They can be forgiven for rebelling against the social and moral order which pays little regard to natural propensities . . ." Chesser pronounces, but a little later we read that nature refuses to be easily thwarted in a rather different matter. "You can remove the possibility of pregnancy, but you cannot remove the strong biological urge to become pregnant and to experience the state of motherhood."

"Surely the individual citizen should have the right to choose between being chaste or unchaste, always assuming this was not detrimental to the society of which he was part," is another of Chesser's demands. But how can this attitude be non-detrimental to society? Pregnancy is by no means the only thing which will affect society. What about the thwarted personalities of those who have thwarted the maternal instinct? Will society be unaffected by them? It seems that, according to Chesser, every coming together of two people on the sexual plane, whether within or without the framework of marriage, is to be considered moral if it is "the expression of a deep and lasting genuine relationship." How can he reconcile with this his statement that pre-marital intercourse so often means little to the boy and much to the girl? Is it then immoral for the boy and moral for the girl? And how is that dilemma to be solved according to Chesser?

A maze of hazy ideas is presented which certainly does not give any guidance. The likely reaction of somebody who reads this uncritically and in search of guidance will be to join in Chesser's slogan that a shocking price is being paid for society's "unforgivable hypocrisy," a slogan unproven by his facts and not accompanied by any constructive proposals. ". . . we must be free to make the choice," Chesser demands. Aren't we free? Each individual makes his or her own choice. Free will is the basis of morality, but does Dr. Chesser think the choice should be made by instinct alone, and not with guidance? Dr. Chesser might think that his article provides guidance, but where would it lead to? In a letter (*Journal*, March 14, p. 714) Dr. Hendry rightly asks: (1) Is the world at large and those about to marry (or not!) in particular likely to be the better for its counsel? (2) Could I as a doctor commend it to my patients? (3) Would I as a father wish my son to accept its standards? The same question concerning parents of daughters seems superfluous.

Dr. Chesser was reported in the daily press as saying in an interview that he was intending to help everybody, not just the good ones. To help the "bad ones" is indeed a duty and the aim of every doctor. It is also the duty of all Christians, all those who follow Christ, who said that we should hate sin but love the sinner. However, how Dr. Chesser thinks he helps the bad ones by his article I am at a loss to see. Surely he must have forgotten in his interview how he emphasized the difference between even condoning human frailty and encouraging it. Helping to overcome such frailty is surely at the very opposite pole to Dr. Chesser's teaching.

A second article which evoked comment was one by Roger Pilkington. "So you're a bride. And are you pregnant, too?" it starts. It is a pity that the sensational beginning, in its coarseness, spoils what on the whole is a good and useful article. No doctor would ask a patient this question in the consulting-room but would wait for her to bring up this matter if need be. Why write for the public in a manner which would be regarded as tactless in direct talk? One of the great truths very well expressed in Pilkington's article is this: ". . . however natural, all mistakes are matters for genuine regret, and where they have a direct effect on another person, then something must be done about them." This is the case of the B.M.A. booklet. A mistake was made when it was published, because whoever reads this booklet, with its proud announcement "Published by the British Medical Association," will assume that it represents the considered view of the doctors of this country. It is now obvious that this is not so with regard to Dr. Chesser's article, and the Chairman of the Council has taken the logical step of stopping distribution. He is to be congratulated on this. It is to be hoped, and I have no doubt, that the Council will endorse his action, even though it will mean that a heavy price will have to be paid for the mistake. Everyone will agree with Dr. Chesser in this, that "principles should not be sacrificed to expediency." I do believe the doctors of this country, and the vast majority of the public in general, are certain of their principles in this matter.—I am, etc.,

Gillingham, Kent. K. F. M. POLE.

SIR,—On reading the sample of letters you have published in the *Journal* of March 14, apropos of Dr. Eustace Chesser's pre-marital chastity article, one observes that the intolerant have—as usual—been very much more vocal than the tolerant. This being so, I wonder whether you will allow a plea for tolerance.

Surely the question at issue here is not whether individual members of the Association agree or disagree with Dr. Chesser. It is whether one group of people, simply by claiming that they have the backing of the established religion, are to be allowed to suppress the sincerely held opinion of another group. No genuine Christian believer is going to be tempted from the strait and narrow way by Dr. Chesser's article, which is written by a humanist for humanists. But the Christians are now a minority in this country, and I fail to see why other people should be silenced in the attempt to preach a straightforward, undogmatic sociology every time their ideas conflict with those of St. Paul. Let each side state its case fairly, and let the people choose. "Getting Married" contains an article on church weddings to counterbalance Dr. Chesser. I, for one, shall be most disappointed and disturbed if this sensible, well-composed publication is not reissued.—I am, etc.,

Bishopbriggs, Lanarkshire. MARGARET LITTLE.

SIR,—I am horrified to find this book "Getting Married" published under the auspices of the B.M.A. Nothing would induce me to let a young person, for whose welfare I were responsible, read it. Its views on morality offend not only Christian ideals but against every canon of decency and good taste.

Isn't there some way of assuring the public that these curious views are those of a minority and not those of the medical profession as a whole? I shall take good care not to recommend *Family Doctor* publications in future unless I have first censored them myself.—I am, etc.,

St. Albans, Herts. MARIE T. O'SULLIVAN.

SIR,—May I, for the information of some of your more excited correspondents, be permitted two brief observations? (1) The B.M.A. is not, so far as I am aware, a religious body, and has no obligation to support the teachings or prejudices of any Church. (2) The suppression of unwelcome facts at the behest of religious or other interested pressure groups is a very old practice and a very unpleasant one.—I am, etc.,

London, N.W.7. ALAN N. COWAN.

SIR,—What an extraordinary collection we B.M.A. members are. Here we have some threatening to resign from the organization if the famous booklet is withdrawn, others who will resign if it is again released. The threat of resignation is nowadays used for the furthering of any and every personal or individual end. It is almost at the level of a music hall joke. Those of us who do any public work at all know only too well that resignation is not the way to deal with any situation. We must stay within the organization and put forward our views. I wonder whether I should threaten to resign unless my fellow members stop threatening to resign.—I am, etc.,

Stanley, Perth. OWEN MCDONAGH.

SIR,—The telegrams and letters received from Divisional secretaries and the letters published in the *Journal* demonstrate that the special committee responsible for publication is out of touch with much popular opinion amongst doctors. Mr. E. Watson-Williams's devastating attack (*Journal*, March 14, p. 715) on the grammar and obscurities of meaning shows clearly that the committee has not troubled to correct careless writing. The harm done to the Association will be incalculable. Resignations represent only a small part of the emotional feeling stirred up against it.

It is difficult to understand the reason for doctors entering the field of marriage guidance. Not only have numbers of doctors been divorced or have unhappy marriages, but also they have, with the exception of anatomy and physiology, received little training in marital matters. All they know has been self-taught. What doctor, or group of doctors, has analysed even 1,000 cases of marital difficulties? The National Marriage Guidance Council has analysed 25,000, seen in the years 1952–4,[1] of the tens of thousands of cases that have applied for help to the counsellors, who are not only married or widowed but must be undivorced, and, whether Christian, Jew, agnostic or atheist, of integrity and high moral character.

Although, after their training, many doctors make excellent marriage guidance counsellors, my own experience, obtained from the examination of numerous doctors appearing before marriage guidance selection boards, leads me to the belief that medical practitioners are not the best group of persons for dealing with marital problems. Would not most of us agree that it is presumptuous to write booklets upon a subject without having been fully trained in it?—I am, etc.,

Clevedon, Somerset. G. DE M. RUDOLF.

[1] *Marriage Counselling*. Wallis, J. H., and Booker, H. S., 1958. Routledge and Kegan Paul, London.

SIR,—I wonder to what extent has the notoriously hypocritical lay press, in pandering to public prurience, encouraged or even stimulated our more ascetic colleagues in the outcry against the de Kok–Chesser booklet? That the medical profession is so easily shocked may perhaps be of interest to students of psychiatry: but surely critics of the publication on its purely literary merits, or even its moral implications, would have been rather more pertinent had they restricted their animadversions solely to factual judgment.

I believe that the only criteria of value in a case of this kind are, firstly, whether or not the book contains any statement which is true or false, or secondly, whether it actually does advocate lascivious behaviour or not. It seems that no one has been able to quote a passage, in or out of context, which is either mendacious or erotic or both.—I am, etc.,

Bilston, Staffs PAUL Z. HAMMET.

SIR,—It is one matter to publish unscientific drivel for home consumption in our *Journal*. We can ignore this and trust this will be ample comment, instead of exposing a Christian concept of life to uncritical changes of bigotry. But to foist a minority prejudice against life and decent standards of human existence on an innocent public is quite another matter, and should not have the backing of a reputable journal. I don't think we are enhancing our reputation for fair unbiased comment by publishing such utter unfounded nonsense as that contained in your happily withdrawn booklet "Getting Married."

My resignation from the B.M.A. would not shake it to its foundation, but every little helps.—I am, etc.,

Leigh, Lancs. W. J. PRENDIVILLE.

*** Editorial and managerial responsibility for the *British Medical Journal* is entirely separate from similar responsibility for *Family Doctor* publications (including, of course, "Getting Married"). In assuming otherwise, Dr. Prendiville makes what appears to be a common mistake.—ED., *B.M.J.*

SIR,—The notoriety achieved by "Getting Married" demonstrates the unwisdom of the entry of the Association into popular journalism. Because the pamphlet is backed by the B.M.A. it is assumed by the public that the views it expresses have the support of the profession as a whole, whereas many of us find these opinions most objectionable. Because the pamphlet was freely available to the public the disagreement it has caused has also necessarily been public. We find

ourselves washing our dirty linen in the launderette, with a great audience outside the window greatly diverted to find us in this undignified pose.

Members of the profession cannot expect to agree about medical matters, let alone the vast field covered by "Family Doctor" and its associated pamphlets. Surely the moral is that our most representative Association should cease forthwith to publish these. Doctors who wish to give this kind of social service could find other agencies through which to do so, without implicating their colleagues.—I am, etc.,

Huddersfield. PATRICIA M. O'SULLIVAN.

Physiotherapy in Arthritis

SIR,—I hope that all doctors in the habit of prescribing physiotherapy will take to heart the findings in the paper by Professor E. G. L. Bywaters, Miss D. E. Hamilton, and Mr. N. W. Please (*Journal*, February 28, p. 542). These authors tried out four forms of physiotherapy, all well known to us as devoid of lasting effect on any form of arthritis, and found them all equally useless.

This is a most important conclusion from an authoritative source. There are to-day some 5,000 physiotherapists working in the National Health Service, many of whom, year in, year out, are doomed to using just these methods on just such cases for part of every working day. At last the dawn of their liberation is discernible.

For the last twenty years I have recommended that radiant heat and infra-red lamps should be banished from all physiotherapy departments. Clearly patients' recovery is retarded if they spend time lying under heat lamps which should have been expended on receiving treatment capable of doing good. Wax baths merely apply local heat in a different way, and are scarcely ever called for. Short-wave diathermy should be reserved for such septic conditions as do not respond adequately to drainage and antibiotics. Faradism can be used to get muscles moving when voluntary control is deficient. Hence none of those methods are applicable to arthritis.

Large saving in patients' time and effort no less than to the finance and transport system of the National Health Service would result from the abandonment of useless methods of physiotherapy. I trust that this timely article will begin the deliverance of the trained physiotherapist from a mass of useless work and enable her to concentrate her skill on cases of responsive disorder.—I am, etc.,

London, W.1. JAMES CYRIAX.

"Poisoning" by Tolbutamide

SIR,—The heading of the letter by Dr. R. D. Lawrence which appeared in your issue of March 7 (p. 644)—"Poisoning by Tolbutamide"—has serious implications, especially as the letter carried with it the authority of the respected doyen of physicians interested in diabetes in this country. The heading was not "Suspected Poisoning" or "Possible Poisoning," which was perhaps all that the author really implied, but plainly and simply "Poisoning." One would expect after such a title a fully documented clinical report leaving no reasonable doubt as to the cause of the "poisoning." In the case reported, however, the evidence hardly justifies this assumption: indeed, the clinical manifestations described are not those usually associated with drug toxicity, and could readily be explained in other ways.—I am, etc.,

Department of Therapeutics, University of Edinburgh. D. M. DUNLOP.

Hypercalciuria

SIR,—In your annotation of this subject (*Journal*, February 21, p. 495) you give a somewhat misleading impression of the work of Dr. E. L. Knapp.[1] She has analysed data on the urinary excretion of calcium in a large number of normal individuals of all ages, many of them having been studied at more than one level of calcium intake. The mean urinary calcium excretion increased with increasing age, and this appeared to be related to increase in skeletal weight, which is represented by total body weight. She also found that at any given age the mean excretion of the group increased with increase in the intake of calcium, and that the increase in excretion with increase in intake appeared to be greater in adults than children.

Dietary factors other than the calcium content had relatively minor effects on calcium excretion, with the exception of ingestion of acids, a ketogenic diet, and diets with a high calcium to phosphorus ratio, all of which increased the urinary calcium. She noted that, for individuals of the same weight eating the same diet, there was a wide range of values for the urinary calcium. She graphed $\frac{\text{urine calcium} \times 100}{\text{intake of calcium}}$ against calcium intake in mg./kg./day, on a log.-log. scale, and was able to define maximum, mean, and minimum values with which the excretion of an individual subject could be compared, given the intake of calcium, the 24-hour urinary calcium, and the body weight. Ward diets from one hospital to another can hardly be regarded as the same diet, and are likely to vary in their calcium to phosphorus ratio as well as in their calcium content, although an approximate calcium intake can be calculated if the intakes of milk and bread (in the British Isles flour is fortified with calcium carbonate and, during the winter months only, with acid sodium phosphate) are known.

In patients with disorders of calcium metabolism the diet is the one factor which is under the control of the investigator. It seems reasonable to work with a standard diet with a known calcium content in any investigation such as my work[2] referred to in your annotation. As Hodgkinson and Pyrah[3] state in their interesting paper, the upper limit of normal calcium excretion on a normal diet cannot be defined precisely, but it is of practical value in situations where an assessment of calcium excretion is required but where a strict control of dietary intake is not practicable. They add that measurements on an accurately controlled intake are preferable. A low calcium diet offers the advantage of more precise definition of the upper limit of normal calcium excretion, and hypercalciuria when present can be diagnosed not only "frequently" but always. It is a clinically useful index of the patient's metabolic status for calcium.[4]

In respect of your observations on the work of Henneman, Benedict, Forbes, and Dudley,[5] I have observed a number of similar patients who have renal calculi, a low serum phosphorus without hypercalcaemia, and hypercalciuria. The serum alkaline phosphatase is normal and the skeleton appears normal on *x*-ray examination. The serum proteins are normal on electrophoresis. I have also observed that these patients have a decreased tubular reabsorption of phosphate (as measured by the ratio of the clearances

of phosphate and creatinine or inulin). One patient was given an intravenous infusion of calcium and responded in a manner similar to the normal subject.[6] However, some patients with a parathyroid adenoma also respond to calcium infusion like the normal subject (data to be published). Two patients with the syndrome described by Henneman and his fellow workers were explored and four normal parathyroid glands were identified. Biopsies were normal.—I am, etc.,

Institute of Clinical Science, Queen's University, Belfast. MARY G. MCGEOWN.

REFERENCES

1 Knapp, E. L., *J. clin. Invest.*, 1947, **26**, 182.
2 McGeown, M. G., *Clin. Sci.*, 1957, **16**, 297.
3 Hodgkinson, A., and Pyrah, L. N., *Brit. J. Surg.*, 1958, **46**, 10.
4 Fraser, R., and King, E. J., in *Biochemical Disorders in Human Disease*, 1957, edited by R. H. S. Thompson and E. J. King. Churchill, London.
5 Henneman, P. H., Benedict, P. H., Forbes, A. P., and Dudley, H. R., *New Engl. J. Med.*, 1958, **259**, 802.
6 Nordin, B. E. C., and Fraser, R., *Clin. Sci.*, 1954, **13**, 477.

Sulphamethoxypyridazine in Dermatitis Herpetiformis

SIR,—Following the medical memorandum by Dr. J. Jefferson (*Journal*, July 26, 1958, p. 209), a trial of sulphamethoxypyridazine in dermatitis herpetiformis was instituted in the Department of Dermatology at Stobhill General Hospital, Glasgow, under the supervision of Dr. A. Girdwood Fergusson, physician in charge. Dr. J. W. Chambers, consultant clinical biochemist, provided laboratory facilities. From previous experience of long-term administration of sulphonamides in chronic ailments, and in consideration of the fact that doses up to 2 g. daily for adults and 1 g. daily for a boy of 3½ years were advised, blood sulphonamide estimations by micro-modification of the method of Bratton and Marshall[1] were performed as an appropriate check on this long-acting and slowly excreted medicament. It was noted with apprehension that the daily dose advised for long-term administration exceeded that recommended by the makers for acute infections, approximating to the less potent and more rapidly excreted sulphapyridine.

Among the first cases treated was a boy aged 5 years whose eruption responded promptly to a dose of 0.5 g. daily, reduced to 0.125 g., but who developed hepatitis two weeks after treatment had been started, the blood level of sulphamethoxypyridazine being at that time 8.6 mg./100 ml. The drug was withdrawn, and, as the patient slowly recovered, his dermatitis herpetiformis relapsed; so, when normal liver function was restored, a trial of sulphapyridine was undertaken, the dosage being gradually increased to 0.5 g. thrice daily, when initial control of the eruption was attained without adverse effects. The blood level of sulphapyridine was then 0.8 mg./100 ml.

Of two fairly well controlled adult cases on whom blood concentrations were estimated, sulphamethoxypyridazine levels were 0.2 and 16.1 mg./100 ml. on doses of 0.5 g. daily and 0.5 g. thrice daily respectively, and at the same time the latter patient was found to have severe hypochromic anaemia (Hb 8.1 g. %; M.C.H.C. 25%). In four patients within the same limits of dosage of sulphapyridine, on the other hand, control was achieved at blood concentrations ranging between 0.7 and 4.6 mg./100 ml.

Perry and Winkelmann[2] in a series of 19 cases of dermatitis herpetiformis and 9 of other complaints treated with sulphamethoxypyridazine had 5 adverse reactions with one death, and they refer to one case of focal hepatitis. They found it difficult to predict maintenance dosage or stable blood levels per unit dose, although, like ourselves, they admitted that control of dermatitis herpetiformis was readily achieved. The adverse reactions they ascribed to the toxic effects of cumulative dosage, and they advised routine assay of blood, concluding that clinicians should balance the benefits of this drug against the risks involved. In agreeing with their conclusions we would add that, whether or not the toxic effects we witnessed were due directly to high sulphonamide concentration, we believe that the remedy which generally gives good results with a low blood level leaving a wider margin for increase and manipulation of dosage is the sulphonamide of choice.—We are, etc.,

JAMES C. P. LOGAN.
MAUREEN CHILDS.

Stobhill General Hospital, Glasgow, N.1.

REFERENCES

1 Bratton, A. C., and Marshall, E. K., *J. biol. Chem.*, 1939, **128**, 537.
2 Perry, H. O., and Winkelmann, R. K., *J. Amer. med. Ass.*, 1959, **169**, 127.

Sympathectomy for Hypertension

SIR,—The paper by Dr. C. P. Newcombe, Mr. H. S. Shucksmith, and Dr. W. S. Suffern (*Journal*, January 17, p. 142) serves to remind us that sympathectomy was the first measure to succeed in prolonging the life of patients suffering from severe hypertension. I cannot believe, however, that Dr. Newcombe and his colleagues would wish to give the impression that any place still exists for this crude mutilation except, perhaps, in the treatment of a backward adolescent in the malignant phase.

Of course much has been learnt about the natural history of hypertension since their follow-up first began some ten years ago. Plainly there were among these 212 patients many whom we would not to-day consider to be suffering from any disease. In some the diastolic pressures were as low as 110 mm. of mercury, while three-fifths of them were women, most of them well over 40 years of age. We know now, chiefly from the work of Bechgaard, that diastolic pressures up to 120 mm. of mercury virtually do not affect the expectation of life of elderly women.

Moreover, in this series, half the patients concerned were in the first two groups of severity. Indeed, over a quarter of them were in group 1. Here vascular damage of hypertensive type in the ocular fundi is almost imperceptible, or at least so slight as to be disputable. Yet 55 of these patients were operated on.

On the other hand, in group 4 there were 83% deaths, more than half of them within the first year. This compares very ill with figures such as those of Smirk and of McMichael (see *Journal*, April 21, 1956, p. 915), both of whom, using ganglion-blocking agents, have claimed a survival rate of over 50% in large groups of malignant hypertensives followed for more than five years.

Nor can we be much encouraged by the symptomatic benefits claimed by Dr. Newcombe and his colleagues. They say that "headache," by which no less than 90% of their patients had been afflicted before operation, was almost always relieved "for a year or more." A similar deliverance was obtained from "dizziness" and "tinnitus." But they add, with great honesty, ". . . in no instance was breathlessness assuaged." All this suggests to me that sympathectomy proved very successful in the temporary relief of psychogenic symptoms. "Blackouts," too, no doubt, were a lot less troublesome for a while. At the same time the operation failed to lessen dyspnoea, a complaint that can nearly always be traced to an organic origin.

It would seem, then, that the best that can be said of the findings in this most interesting follow-up is that sympathectomy did not prove immediately fatal to any

of those patients in whom life expectation would otherwise have been normal, but that its benefits to those with advanced hypertensive disease, though undoubtedly a great improvement on anything that had been done before, can now be seen to be much less than we can confidently expect from treatment with the modern autonomic paralysant drugs.—I am, etc.,

Blackpool. I. McD. G. STEWART.

Preparation for Hysterectomy

SIR,—How delightful to read Mr. W. G. Mills's letter (*Journal*, February 14, p. 436). Here, obviously, is a gynaecologist who takes a keen interest in the results of hysterectomies, conducting a personal follow-up of his patients, who are seen three to ten years later. He also appreciates the importance of pre-operative guidance. Yet even he, with all his care and attention, admits nine of his 59 patients were unsatisfied with the results and 10 patients had sexual or marital difficulties. It is sad that he considers my findings uncomplimentary, for I was seeking to call attention to the undoubted aftermaths, which he corroborates, and at the same time to make a plea for co-operation between the general practitioners and gynaecologists to decide whose is the responsibility for the pre-operative preparation and post-operative guidance to both husband and wife. My opening and closing remarks at the Royal Society of Medicine[1] express my view concisely. "Not all hysterectomies end in tragedy, but a great deal can be learnt from those which do. . . . Let us recognize that there are aftermaths and that prevention is always better than cure."—I am, etc.,

Edmonton, London, N.18. KATHARINA DALTON.

REFERENCE

[1] Dalton, K., *Proc. roy. Soc. Med.*, 1957, **50**, 415.

Dystonic Reaction to Perphenazine

SIR,—When Drs. R. D. Montgomery and V. L. Sutherland state that their confidence was shaken in the diagnosis of an iatrogenic disorder, I sympathize with them. In their case report of an acute dystonic reaction to perphenazine (*Journal*, January 24, p. 215) they emphasize the dramatic nature of the reaction. I should like to record my surprise when I was phoned by a lady who complained of lockjaw.

When she arrived at my surgery she was in acute distress, and with some difficulty explained that some nine hours previously she had begun to experience painful spasms of the jaw which lasted from five to ten seconds. Although these spasms began on the left side, they increased in length and intensity, and when I saw her her jaws were tightly and painfully clenched together. During the next hour the painful spasms alternated with exaggerated yawns which were quite involuntary.

She gave a history of pricking her finger with a needle some three weeks previously, but she denied any other abrasion and could think of no other significant fact. In her distress she only wanted relief, and, in being forced to consider tetanus, I administered a test dose of A.T.S. She then mentioned that she had taken some tablets during the morning. She had taken these before during last year. These were bought in a town some 30 miles (48 km.) away, but, although the hour was late, the chemist was contacted and he was able to establish that the tablets were "trilafon" (perphenazine), 8 mg. She had in fact taken four of these tablets during the morning, which was in excess of the dose recommended, and her symptoms had begun a few hours later. Although trismus was not mentioned as a common side-effect, I made a diagnosis of drug toxicity and gave her pethidine and one of the new striped-muscle relaxants. Within an hour her symptoms were markedly relieved and never returned.

In a personal communication, the medical director of the supplier in Montreal stated that quite a number of similar cases had been reported and that such a sequence of events had been noticed after a dose of 4 mg. Some patients can be maintained on a dose as high as 192 mg. per day for long periods of time, and it would appear that there is a true hypersensitivity in some individuals. Although some painful and alarming symptoms have unfortunately resulted in some cases from the drug, no serious results have been noted. Antiparkinsonian drugs are of use in relieving spasms.

As a footnote I must add that two weeks later I prescribed the drug for a severe case of hyperemesis gravidarum. After 24 hours or more, having taken only 16 mg., the patient re-entered my surgery with inability to talk, slurring of speech, and with such a marked degree of neck retraction that she was unable to vomit into the bowl held before her.—I am, etc.,

Deep River Hospital, Ontario. JOHN R. SANDFORD.

SIR,—In view of the acute toxic reaction to perphenazine described by Drs. R. D. Montgomery and V. L. Sutherland (*Journal*, January 24, p. 215), the following case is of interest.

The patient, a lady of 77, was admitted to hospital for observation after swallowing approximately 30 tablets (4 mg. each) of "fentazin" (perphenazine). The tablets had been prescribed for a state of agitated depression and had been taken in an impulsive gesture. On admission she was drowsy but fully conscious, and there was no physical abnormality. Pulse rate was 80 and blood pressure 176/106. No protein and no sugar were found in the urine.

On the following day the blood pressure was 190/110, and the results of blood examination were as follows: Hb 99%; E.S.R. 1 mm. in the first hour; R.B.C. 4,980,000/c.mm.; W.B.C. 6,250/c.mm.; tests for liver function showed no impairment.

She was transferred to a mental hospital for treatment of her depression, and her further progress was uneventful.—I am, etc.,

The Royal Infirmary, Edinburgh. W. D. BOYD.

Blood-grouping Technique

SIR,—I have just read the M.R.C. Memorandum No. 36 on blood grouping[1] which came out last year. It has, of course, been compiled by a panel of experts, and the techniques described are recommended as a result of very considerable experience.

However, suppose a duty pathologist or technician is called to provide two pints (1.1 litres) of blood which may be required for an ungrouped patient. Suppose, further, that, being conscientious, he resolves to follow the recommended technique exactly. He will then set up no less than 38 tubes; the grouping and subsequent cross-matching together will involve him in at least 86 separate measurements of small quantities of fluid into and out of these tubes (apart from the final readings); and the readings will include, *inter alia*, 20 microscopic examinations as well as the tedious thrice washing of four lots of cells in the Coombs procedure. The cross-matching alone will hardly take less than three hours.

Now, I doubt whether many hospital laboratories in this country do in fact adhere to this ritual, but I suspect

that if they did we would see evidence of diminishing returns. By endeavouring to be 100% safe, I feel there would be risks not only from gross errors due to the complexity of the tests, but also from undue delays in the availability of the blood to the patient, from having to start again after a mistake had been made or suspected. Further, the prospect of having to cope with two or more such investigations asynchronously becomes quite appalling.

Even during the day, can many laboratories away from the main centres afford the "man-hours" for such tests?

What risks are we trying to avoid? How many fatal reactions have occurred due to incompatibilities other than those of the readily detected ABO or gross Rh (D) types? (I appreciate that in girls and women of the child-bearing age other considerations do come in.) Is blood transfusion more lethal in those hospitals that do not employ the more complex tests? With due deference to the experts, who do after all work in rather special conditions, I ask whether we are not becoming a little obsessional in this matter, and wonder whether much simpler methods, carefully and unhurriedly performed, are not as safe, or safer, in the ordinary laboratory, at any rate for male recipients.—I am, etc.,

Great Missenden, Bucks. HUGH G. PENMAN.

REFERENCE

[1] *The Determination of the ABO and Rh (D) Blood Groups for Transfusion*, M.R.C. Memorandum No. 36, 1958. London, H.M.S.O.

Intravenous Needle for Introduction of Polythene Tubing

SIR,—Dr. R. Vaughan Facey's method of inserting polythene tube into a vein (*Journal*, January 31, p. 304) has the disadvantage that the needle used must be wider than the tube. I have found the non-surgical technique described by Dotter and Smith[1] to be very satisfactory. In this method (see Fig.) the tubing outside the needle corresponds to a cannula and the needle to a trocar, consequently the tubing inserted is of a wider bore than

that of the needle. I have found that a large-sized Guest cannula and needle are ideal for introducing the tubing, as the cannula can be fitted into the free end of the tubing and the drip tube attached to it. Insertion of the needle and tubing into the vein is helped by attaching the needle to a syringe. This prevents blood escaping from the needle once it is in the lumen of the vein. I have used this method with great success.

I would like to thank Dr. T. E. Gumpert for giving permission to use the method on patients in his wards.

—I am, etc.,

The Royal Hospital, Sheffield. W. STACEY FURNISS.

REFERENCE

[1] Dotter, C. T., and Smith, J. R., *Circulation*, 1958, **18**, 640.

Outlook in Cancer

SIR,—Contributions from Sir Gordon Gordon-Taylor are always of the utmost interest, but I wonder if Sir Gordon would allow me to draw from his recent Mitchell Banks lecture on "The Incomputable Factor in Cancer Prognosis" (*Journal*, February 21, p. 455) a moral rather different to what he had perhaps intended. Might not the "incomputable factor" to which Sir Gordon refers be taken as evidence for the prosecution against the whole surgical policy pursued by his great masters? The surgical philosophy of these great men—of Halstead, Pearce Gould, Thomas Miles, and the rest—was a comparatively simple one based on Virchow's cellular pathology: the wider the excision, the greater the chance of success. Can we now accept this as really true?

Their philosophy was supported by series after series of rates of survival down the years, but, if these documents are regarded quite dispassionately, one must admit that they are generally inadequately controlled and therefore of doubtful value. A woman does not necessarily survive 30 years because she has had a radical mastectomy. She might have survived just as long following a simple removal of the lump, or even without any surgery having been performed at all. It is an all-too-frequent experience to see a woman, operated upon for a lump which she insists has been present for many years, riddled with metastases six months after her operation.

The outlook in cancer is utterly unpredictable, and to this unpredictability there would seem to be two answers. The first is to take full advantage of all modern advances in anaesthesia and resuscitation and to perform ever more and more radical excisions, until one hardly knows which half of the body to keep. The second, and surely more rational, answer is to accept the inevitable fact that surgery cannot cure.

The cases which Sir Gordon describes are exceptions and it is for this very reason that they are counted worthy of description. We must not base our surgical policy on exceptions. "Je les opère, mais je ne les guéris pas," was an oft-repeated cry of the great Professor Hartmann. If, then, we can offer little in the way of cure, surely it is at least incumbent upon us to avoid needless mutilation. In the case of cancer of the breast, for example, when the whole rationale of radical mastectomy is so insecure, surely it is fairer to our patients to plan our surgery with at least some thought of their future comfort? Sir Gordon once gave as his answer to cancer—he will forgive me if I misquote, but it is several years ago—"a sharp knife, a stout heart, and boundless optimism." With the unpredictability of cancer it is the patient who needs the stout heart and the boundless optimism, and may we not temper the wind to the shorn lamb by seeing that not all our knives are quite so sharp?—I am, etc.,

Farnham Common, Bucks. ROBIN BURKITT.

Hypotension after Noradrenaline

SIR,—In 1954 we reported a case of phaeochromocytoma in which the patient had hypotension (blood pressure 90/65) between the paroxysms of hypertension.[1] The tumour when removed was found to contain mostly noradrenaline, the ratio of noradrenaline to adrenaline being 20:1. This clinical observation fits in well with the experimental results of Professor J. H. Burn and Dr. M. J. Rand (*Journal*, February 14, p. 394). If their hypothesis is correct one would expect that there would be variation in the resting blood pressure in such a case,

the pressure following a paroxysm being lower than that preceding one. We did not record serial readings of the resting blood pressure in the case we reported, but we think it would be of interest to do so in future cases.—We are, etc.,

I. MCLEAN BAIRD.
HAROLD COHEN.

Barnsley, Sheffield.

REFERENCE

1 Baird, I. M., and Cohen, H., *Lancet*, 1954, **2**, 270.

SIR,—The article by Professor J. H. Burn and Dr. M. J. Rand (*Journal*, February 14, p. 394) is a very valuable one that I believe takes up only part of the problem of blood pressure fall during and after noradrenaline infusion.

We have found that infusion of noradrenaline at moderately high doses into the unanaesthetized or pentobarbital anaesthetized dog did not produce a lasting elevation of blood pressure, but that within 30 to 60 minutes after the start of an infusion the blood pressure returned to baseline levels. At this time the cardiac output determined by dye dilution method has fallen some 50%. If at this time the infusion is stopped there will be a further fall in blood pressure to very low levels and an even more precipitous fall in cardiac output. These results are obtained with rather high doses, in the range of 7 to 60 gamma per kilogram per minute. For technical reasons studies of blood volume have been unsatisfactory, but previous workers have shown that the blood volume does decrease markedly in similar situations.

I would therefore raise the question that part of the marked fall in blood pressure after discontinuing noradrenaline may be due to reduced blood volume. The ingenious explanation by Professor Burn may well be another aspect of the problem.—I am, etc.,

The University of Mississippi, Jackson, Mississippi. HERBERT G. LANGFORD.

Methyl Phenidate in Psychiatry

SIR,—The value of Dr. J. E. A. Bartlet's conclusion (*Journal*, February 21, p. 481) that 26 out-patients treated with methyl phenidate by mouth showed "a marked overall improvement" in their depression is limited by the absence of attempt at statistical control of the results. We studied this drug in depressive states, and published a double blind controlled trial on 45 patients.[1] We concluded that "in doses of 10–20 mg. b.d. methyl phenidate was shown to have no advantage over a placebo in the treatment of depression or associated symptoms." In this study, as well as clinical assessment, the patients were assessed with a number of psychological tests, which confirmed the clinical appraisals.—We are, etc.,

ASHLEY A. ROBIN.
S. WISEBERG.

Runwell Hospital, Near Wickford, Essex.

REFERENCE

1 Robin, A. A., and Wiseberg, S., *J. Neurol. Neurosurg. Psychiat.*, 1958, **21**, 55.

Asphyxia with Nitrogen

SIR,—I feel that it should be put on record that not everyone would agree with Dr. Michael A. Weller's explanation of the subconjunctival haemorrhages found in his patient who used nitrogen instead of air in his self-contained under-water breathing apparatus (S.C.U.B.A.) (*Journal*, February 28, p. 559). From Dr. Weller's description of the events which followed the discovery of this unfortunate man at the bottom of the swimming-pool, it seems that he was brought to the surface quickly but only landed and resuscitated after some little time had elapsed. During this time the mouthpiece was firmly in his mouth. As his last breath had been taken from his gas cylinder at a pressure equal to that at the bottom of the pool, it means that he had compressed gas in his chest for quite a while after being rescued.

His intrathoracic pressure would have been greater than atmospheric by 6 ft. (1.8 mm.) of water, or about 140 mm. of mercury. In order to maintain the circulation, the venous pressure would rise to this level, quite high enough to produce subconjunctival haemorrhage (cf. in whooping-cough). It is difficult to see how "suction" could develop under his face mask, if this was of the conventional type covering both nose and eyes, as there would be free communication with the air in the mouth and lungs. In effect, it is likely that he was suffering from traumatic asphyxia—the compression in his case being from within the chest and not, as is more usual, from without.—I am, etc.,

Royal Devon and Exeter Hospital, Exeter. G. H. HALL.

Accidental Haemorrhage

SIR,—Dr. F. A. L. da Cunha's article on accidental haemorrhage treated by caesarean section (*Journal*, February 28, p. 551) was most interesting. He advocates immediate caesarean section in cases of accidental haemorrhage when foetal heart sounds are present at the time of admission, and with a minimum of delay where resuscitation is necessary for reasons of shock.

He should perhaps have stressed too that caesarean section should be delayed in the presence of a low fibrinogen level of the blood until this defect has been corrected, because, if caesarean section is carried out in the presence of hypofibrinogenaemia or afibrinogenaemia, troublesome and uncontrollable oozing may be encountered at operation that may even prove fatal, as pointed out by Barry *et al.*[1]—I am, etc.,

Maternity Hospital, Cambridge. FERNAND ESPITALIER-NOEL.

REFERENCE

1 Barry, A. P., Feeney, J. K., and Geoghegan, F. J., *Brit. med. J.*, 1955, **2**, 12.

Immunization Programmes

SIR,—I have been most interested in the correspondence proceeding in the *Journal* concerning the pros and cons, in immunization programmes, of combined versus separate inoculations.

I must support the combined method, because I believe that it is the only practicable one in any large immunization programme. I am glad that the local authority for which I work personally has continued to use combined whooping-cough and diphtheria immunization, and I note that a neighbouring local health authority that for a time followed advice that had been given to change to separate inoculations has now reverted to the combined system because of the great difficulties that were encountered.

I think also that it might be of interest to the readers of the *Journal* to note the sort of programme that is being carried out in Canada. From 1952 to 1953 I

worked in British Columbia as medical director of the South Central Health Unit, and inaugurated an immunization programme in 1952 which has since been developed. I have just received the 1958 annual report of this Health Unit in which the following schedule of immunization from infancy to school age is outlined, as generally practised in the 17,000 square mile area covered by this health unit:

3 months	Diphtheria, pertussis, tetanus
4 months	Diphtheria, pertussis, tetanus
5 months	Diphtheria, pertussis, tetanus
6 months	Smallpox
7 months	Polio
8 months	Polio
1st year	Diphtheria, pertussis, tetanus; Polio
3rd year	Diphtheria, pertussis, tetanus
Grade I (school: age 6)	Diphtheria, tetanus; Smallpox
Grade V (school: age 11)	Diphtheria, tetanus; Smallpox
Grade IX or X (school: age 16)	Diphtheria, tetanus; Smallpox

I am particularly interested to note how the immunization against smallpox has been stepped up, and I feel that this is a point to which we should give more attention in this country.—I am, etc.,

Salisbury and Wilton R.D.C. Offices, Salisbury. D. M. LISHMAN.

SIR,—I am sure that the majority of medical officers will welcome the brave attempt by your correspondents—medical officers of health of certain metropolitan boroughs—to rationalize the present system of timing prophylactic injections in infancy (*Journal*, February 7, p. 362), but I disagree with their recommendations on two points.

Firstly, vaccination against smallpox in the first month of life. The neonatal period has been defined[1] as "the time of adjustment to separate existence," and I feel that, although it has been demonstrated that neonates are capable of producing an adequate antibody response, it is unnecessary to burden their relatively undeveloped physiological machinery with a prophylactic insult which could well be left until the fifth or sixth month. Another factor is the occurrence of infantile eczema, which is often not manifest until the child is a few months old. Eczema developing after vaccination is always a source of embarrassment, while known eczema sufferers would not normally be vaccinated at all.

My second objection is the postponement of the diphtheria–tetanus inoculations until the second year, as I consider that these could be given between the second and third poliomyelitis injection—i.e., between 7 and 14 months, when mothers are usually making regular attendances at maternity and child welfare clinics.—I am, etc.,

Chingford, Essex. GEOFFREY POOLE.

REFERENCE

[1] Hinden, E., *A Primer of Paediatrics*, 1957. Macdonald, London.

Trifluoperazine in Schizophrenia

SIR,—In their article on "stelazine" (trifluoperazine dihydrochloride) in paranoid schizophrenia (*Journal*, February 28, p. 549), Drs. R. Macdonald and T. P. S. Watts emphasized the improvement in the capacity for social living produced by the drug. This is the experience gained after a trial of trifluoperazine at this hospital, the results of which are briefly reported.

As part of the trial a group of 17 chronic schizophrenics of the most deteriorated type were selected. Some were paranoid and some catatonic, but all showed a complete lack of any social contact with fellow patients, nurses, and relatives. Their illnesses had lasted for periods of from 6 to 34 years, and most of the patients were receiving maintenance doses of chlorpromazine or reserpine up to the beginning of the trial. Trifluoperazine, 10 mg. daily, increasing gradually to 40 mg. daily was given in a single morning dose, and the trial has now lasted for five months.

Contrary to the findings of Forrester,[1] side-effects were not troublesome. Mild and easily controlled Parkinsonism occurred in six of the patients, and in no case was it necessary to discontinue the drug.

In view of the fact that 11 out of these 17 deteriorated patients were able to reform social contacts to the extent of improving their appearance and habits, engaging in occupational therapy, and being taken home on leave by relatives, I can confirm that trifluoperazine dihydrochloride is a valuable drug in the management of chronic schizophrenia.—I am, etc.,

Whittingham Hospital, Lancashire. D. P. OAKLEY.

REFERENCE

[1] Forrester, M. E., *Brit. med. J.*, 1958, **2**, 90.

Rubella in Pregnancy

SIR,—Dr. Noel H. Moynihan (*Journal*, February 28, p. 588), under the heading "The Art of Consultation," has done a service in drawing attention to the fifth James Mackenzie lecture to the College of General Practitioners, reported in your issue for November 29 (p. 1349).

Krugman and Ward,[1] of New York, quote Lundström[2] on the Swedish epidemic of rubella of 1951, which they call "a well-controlled prospective type of investigation." Here 17% of the children born to 1,067 women who had rubella during the first four months of pregnancy were stillborn, premature, or affected by congenital defects; the corresponding figure for 2,226 women not affected by rubella was 6%. If, however, as Krugman and Ward point out, the premature living infants are omitted from the figures in both groups the percentages would be altered to 10.4 in the rubella-infected group compared with 3.2 in the uninfected group.

The result of carrying out the advice approved in the James Mackenzie lecture would mean the killing of approximately nine healthy foetuses to prevent the birth of one abnormal child. Too much publicity cannot be given to prevent such unbalanced views resulting in mischievous action.—I am, etc.,

Bunbury, Cheshire. HERBERT TERRY.

REFERENCES

[1] Krugman, S., and Ward, R., *J. Pediat.*, 1954, **44**, 489.
[2] Lundström, R., *Acta pediat.*, 1952, **41**, 583.

Cancer Survival Rates

SIR,—One reads with amazement mingled with irritation the letter by Dr. J. A. H. Waterhouse (*Journal*, February 21, p. 511), who tortuously agrees with the views expressed by Professor Sidney Russ (*Journal*, December 27, p. 1593) on the advisability of avoiding correction factors to the crude survival rates in the presentation of the results of treatment of malignant disease. Dr. Waterhouse cavils, however, and tries to convince the reader that an anomaly arising from statistical treatment, such as a 10-year survival rate

greater than its associated 5-year rate, is desirable as it is "a salutary reminder of the deficiencies of the data upon which it is based."

While this way of reasoning is indeed salutary, as it clearly typifies the approach in these matters of many statisticians, it certainly is most unfair to those (surgeons and radiotherapists alike) who toil and sweat and then have to watch the results of their labours bedevilled by arithmetical acrobatics which are unscientific and untenable on any score. We sympathize with Dr. Waterhouse for the errors which crept into his cancer reports, and which he candidly admits. We cannot, however, accept his suggestion of the adoption of half-hearted measures such as the revival of "the median survival time." The unadulterated crude survival rates still represent perhaps the least burdened raw material of data devoid of statistical elaborations, and those working in the cancer field would like to see its deficiencies made good unequivocally. Professor Russ has again put us in his debt by drawing the attention to the problem of a saner presentation of cancer survival rates.—I am, etc.,

Department of Radiotherapy, General Hospital, Northampton. B. JOLLES.

Hydroxydione Injection Technique

SIR,—It was most interesting to read the suggestion by Drs. John W. Dundee and Leo. McArdle (*Journal*, March 7, p. 644) that they had used the reactive hyperaemia which followed 3–5 minutes' arterial occlusion of the arm to facilitate a rapid flushing-out of the veins when administering a new intravenous barbiturate.[1] Also, that the incidence of post-anaesthetic venous thrombosis appeared to be greatly reduced by this method. We will certainly follow up their suggestion that a similar technique might be useful when administering hydroxydione.

In the same issue of the *Journal* (p. 645) Drs. J. M. Hall and A. M. Hutton inferred that the incidence of venous thrombosis mentioned by us (17–20%) as following the use of 5% thiopentone was unnecessarily high, as they found an incidence of only 0.5% in their series during the first 48 hours after operation. Our figures were taken from the unpublished findings of a committee (of which one of us was a member) of 24 anaesthetists which met some 15 years ago. Among other things it compared the incidence of post-operative venous thrombosis as between thiopentone and another thiobarbiturate. In this investigation, however, all the cases were followed up for at least a week.

One of us (A. H. G.) has been anaesthetized with thiopentone on six occasions. After the first three (1940, 1945, and 1946) varying degrees of venous thrombosis developed. In no instance was this noticeable for several days, although—regrettably perhaps—it was looked for. This personal experience as a patient may lend support to a suggestion once made by Drs. Hall and Hutton[2] that it was the spirit used for "sterilizing" syringes in those early days of intravenous anaesthesia which was to blame. This may be. On the other hand, Drs. Hall and Hutton might find their statistics somewhat less comforting if they followed up their cases for a week instead of for 48 hours.—We are, etc.,

London, S.E.5. A. H. GALLEY.
London, S.W.3. L. H. LERMAN.

REFERENCES
1 Dundee, J. W., *Brit. J. Anaesth.*, 1957, **29**, 440.
2 Hutton, A. M., and Hall, J. M., *Anaesthesia*, 1957, **12**, 467.

Obituary

IVY MACKENZIE, M.D., F.R.F.P.S.

Dr. Ivy Mackenzie, one of Glasgow's most distinguished consultants, died on March 7 at the age of 81.

Ivy Mackenzie was born at Ballikinrain, Stirlingshire, on June 11, 1877. He was educated at the local village school at Killearn and at Glasgow University. After taking degrees in pure science and in arts, he graduated M.B., Ch.B. in 1902 and obtained his M.D., with honours, in 1912; he was elected a Fellow of the Royal Faculty of Physicians and Surgeons in 1917. After graduation he worked in Dresden as voluntary assistant to the late Professor C. G. Schmorl, who later became one of his lifelong friends. Though ultimately destined to become a clinician, he retained his interest in anatomy throughout his life, and was intimate with many distinguished anatomists and pathologists of the period, including Keith, Flack, Turnbull, and Aschoff. Perhaps his interests were first directed towards clinical medicine by his namesake, Sir James Mackenzie, who was also numbered among his personal friends. He was appointed visiting physician to the Victoria Infirmary, Glasgow, at the unusually early age of 36. Concurrently with this post he was visiting physician to the Eastern District Hospital, where he had charge of the mental observation wards. The first world war found him in charge of wards in the Military Hospital at Bellahouston, where he was interested in the problem of shell-shock. Later, he became well known in medico-legal circles and was recognized as an outstanding witness both in criminal and civil actions. After retiring from the Victoria Infirmary on reaching the age limit, he was appointed consultant at Stobhill Hospital, where he had wards devoted to encephalitis, a post which he held until his death.

In early life Ivy Mackenzie suffered from poliomyelitis, which left him crippled. This handicap in no way limited his energy, and his friends marvelled at the amount of work he could get through. A man of wide interests, with original views and an inquiring mind, he did a vast amount of research; for many years he ran his own private laboratory with a technician whom he had trained personally. His publications up till 1934 numbered 56 and included contributions to anatomy, pathology, bacteriology, cardiology, neurology, and psychiatry. His last communication was a film demonstration to the Royal Society of Medicine in 1949 dealing with somatic movements of the prematurely born foetus. His interests were not confined to medicine or science; at one time he was chairman of the Scottish Liberal National Association.

Ivy Mackenzie was a staunch friend, and many in Glasgow and elsewhere owe a great deal to his guidance and helping hand. He was adept at judging character, and he had a strong sense of moral and spiritual values. His keen sense of humour frequently emerged during the thrust and parry of cross-examination in the witness-box, and also in the discussion of philosophical and political questions with his intimate friends. He was a Commander of the Venerable Order of St. John of Jerusalem, and played a not inconsiderable part in the establishment of the Foundation Hospital in Glasgow. He leaves a widow, a son who holds a consultant appointment in Guy's Hospital, and two daughters, to whom we extend our deepest sympathy. —A. A. F. P.

E. H. RINK, B.M., F.F.A. R.C.S.

Dr. E. H. Rink, consultant anaesthetist to Guy's Hospital, died at Edenbridge Hospital, Kent, on March 6. He was 54 years of age.

Ernest Herrmann Rink was born on January 22, 1905, and was educated at Tonbridge School and Magdalen College, Oxford, before entering Guy's Hospital in 1927 to complete

his clinical training. He qualified M.R.C.S., L.R.C.P. in 1930, and later the same year obtained the degrees of B.M., B.Ch. After holding a number of house appointments at Guy's he became a demonstrator of anaesthetics in 1933. In the following year he became non-resident anaesthetist at Guy's, being appointed to the consultant staff of the hospital in 1935. In the same year he obtained his D.A. diploma. During the second world war he served in the R.A.M.C., at first in the Middle East as an anaesthetist, and at a later date he became adviser in anaesthetics to an Army Group. On his return to civil life he played a great part in teaching many ex-Service registrars the principles and practice of thoracic anaesthesia. He was admitted F.F.A. R.C.S. in 1948.

"James," as he was always known, was an erudite, instructive, and entertaining companion, as he was a widely read man of considerable wit in which there was no malice. On request he was ever ready to give advice, which was invariably sound, to his juniors and his friends in anaesthesia. He had an excellent ear for music, which was one of his great enjoyments. His main interest was in thoracic anaesthesia, and he will always be remembered for the work he did during the early stages of the development of cardiac surgery at Guy's Hospital. It was with great reluctance that he gave up cardiac anaesthesia a few years ago on the advice of his physicians. He will be greatly missed by his colleagues, and will leave a gap which will not readily be filled. To his widow and two sons we offer our sincere sympathy in their bereavement.—A. M. H.

J. C. N. writes: Dr. E. H. Rink's many friends will have heard with sorrow of his untimely death. As one of the oldest of his medical friends since undergraduate times, I should like to add a word of appreciation of his many good qualities. Rink disliked his real name, which was Ernest, and was almost universally known by his professional intimates as "James," a name which had been given him in the family circle. His oldest Oxford friends always knew him as "Uncle," a name which he had invented for himself and which suited him very well, for his manner was and always remained a benevolent and an avuncular one. In his early days he was essentially a Londoner, although more recently he took to living in the country. His tastes and recreations were those of a Londoner. A child in the first war years, and reaching maturity in the twenties, he had and retained the outlook and mode of speech of that epoch. As an undergraduate he showed considerable aptitude in dealing with scientific apparatus, and as partners in Sherrington's famous "cat class" he looked after that side of our experiments while I did the operative surgery. After qualification he took to anaesthetics almost from the start, and became a safe, careful, and generally excellent anaesthetist. The fact that he played his part in the earliest intracardiac operations performed at Guy's is sure evidence of his ability and professional courage. During the years of the second world war, although the most unmilitary of men, he served for the duration, and in the latter stages of the war he carried out most efficiently and tactfully his duties as an adviser in anaesthetics. In character, and even in appearance, he changed very little with the passing of the years. Although self-depreciating to a degree, it was apparent to those who knew him well that he had considerable underlying ability in other than purely professional respects. He liked good music and played the piano well, and he also had an appreciation of the arts and literature above the average. His old friends will feel a sense of loss at his passing.

ARCHER IRVINE-FORTESCUE, D.S.O., M.B., Ch.B.

Colonel Archer Irvine-Fortescue, who became a Deputy Lieutenant of Kincardineshire after his retirement from the R.A.M.C., died at Aberdeen on March 10.

The son of Dr. William Irvine-Fortescue, of Kingcausie, Aberdeenshire, Archer Irvine-Fortescue was educated at Aberdeen Grammar School and at Aberdeen University, where he graduated M.B., Ch.B., with honours, in 1904. His first appointment after graduation was that of curator of the Royal Herbarium, Calcutta, and in 1907 he began a distinguished career in the R.A.M.C. which took him to many lands. In the first world war he saw service in France, Italy, and North Russia, being mentioned in dispatches four times, and receiving the D.S.O. and the Russian Imperial Order of St. Stanislaus for gallantry in his evacuation of the wounded in the retreat from Shenkursk.

From 1919 to 1921 he was a member of the Anglo-Persian Military Commission, and the Shah of Persia conferred upon him the Order of the Lion and Sun for his services in dealing with a severe epidemic of typhus in a camp for Bolshevik prisoners near Tehran. The prisoners were dying at the rate of twenty a day until his prompt and vigorous measures stamped out the disease and saved the lives of over 400 potential victims. In 1923 he received a medal for his services in the Waziristan campaign; from 1926 to 1929 he was Inspector of Medical Services, Iraq Army; and he was decorated for his work in the Kurdistan campaign. From 1929 to 1932 he was in command of the military hospital at Edinburgh Castle. Wishing to improve his knowledge of financial matters, he took the degree of Bachelor of Commerce at Edinburgh University in 1933. After further service in India, he retired in 1937, his last Service appointment being that of A.D.M.S. in the Rawalpindi District. When he retired to Kincardineshire he became a county councillor, justice of the peace, and later Deputy Lieutenant. Before the second world war he was appointed A.R.P. Officer and public relations officer for Territorial Army recruiting in the north-east. In 1939 he was recalled to service as deputy director of medical services, Scottish Command. At the age of 60, in 1940, he was appointed A.D.M.S. No. 4 Liaison Office (the Polish Military Mission), and took up the study of the Polish language with avidity. He was already a qualified interpreter in nine languages, and had a very fair knowledge of many more. He was continually acquiring new languages, and became proficient in Spanish at the age of 72, while he began to study Norwegian at 77, in preparation for a visit to that country. In 1941 he was awarded the Polish Medical Services Decoration, and in 1946 he was appointed A.D.M.S. of the Polish Resettlement Corps, with headquarters in London, where he was in complete charge of medical arrangements for all the Polish forces in this country, retaining the post until he retired in 1949. A colourful and forceful personality, he found in the Army Medical Services a career to suit his great talents.

Colonel Irvine-Fortescue was the fourteenth laird of Kingcausie. His ancestor, Henry Irvine, acquired the lands in 1535, and they have remained in the family ever since. He leaves a widow, a son, and a daughter.

TOM HARE, M.D., B.V.Sc., M.R.C.V.S.

Dr. Tom Hare, formerly professor of pathology at the Royal Veterinary College, died at his home at St. Albans on March 17.

Tom Hare was born on October 8, 1895, and was educated at Loughborough Grammar School and the University of Liverpool, where he enrolled as a veterinary student in 1912. He served throughout the first world war in the Cheshire Regiment, attaining the rank of captain. Shortly after demobilization he qualified as a veterinary surgeon, but he carried on with the study of medicine at Liverpool and graduated M.B., Ch.B. in 1924. As a student he took a prominent part in university affairs, being president of the Guild of Undergraduates at Liverpool, and chairman of the Inter-varsity Athletic Board of Great Britain and Ireland. Soon after graduation he was appointed Thelwell Thomas fellow in surgical pathology at the University of Liverpool, and later he held the Holt fellowship in pathology. He proceeded to the M.D. in 1926. After a short period of work at the Lister Institute Dr. Hare became professor of pathology at the Royal Veterinary College in

1927. Six years later he was appointed director of the Veterinary Research Laboratories.

Although for most of his professional life Dr. Hare was engaged in veterinary research and won for himself a leading place in the veterinary profession, yet he retained an abiding interest in medicine and was an active member of the B.M.A. Chairman of the St. Albans Division in 1938–9, he was a member of the medical war committee of the Mid-Herts Division throughout the second world war, and in 1952 he gave a most informative and entertaining address to the same Division on "The Practice of Medicine for Animals." This was published in the *British Medical Journal*. He had been a member of council of the British Veterinary Association and of the Royal College of Veterinary Surgeons.

Dr. Hare was keenly interested in the life and works of William Harvey and was a past-president of the Harveian Society. His presidential address was on "The Tudor Ancestry of Dr. William Harvey," and for some time before his death he had been writing a book on Harvey.

Dr. Hare was married and is survived by his widow, a son, and four daughters.

Mr. A. B. ORR writes: My association with Dr. Tom Hare since 1927 gave me the privilege of seeing and helping in the development of the work for which his name is probably most widely known in the veterinary profession—the syndromes produced in animals by infection with the β-haemolytic streptococcus, either alone or associated with parasitic bowel infections. The very complete case records which he invariably kept formed the basis of the papers on the subject published from time to time in the *Veterinary Record* and the *Veterinary Journal*. It was characteristic of him that he always devoted immense care, patience, and time in eliciting a full case history; this he regarded as essential for a sound clinical diagnosis, and he was sharply critical of modern trends in both the medical and veterinary professions which tended to minimize the importance of this part of the clinician's work.

To those who knew him well it was apparent that a deep interest in the welfare of the veterinary profession and a firm belief in its dignity were perhaps the most powerful influences affecting Dr. Hare's thoughts and actions. He always emphasized the importance of the confidential nature of the relationship between doctor and patient or veterinary surgeon and client, and he regarded with alarm, and strongly opposed, the encroachment of officialdom into private practice as tending to destroy or at least weaken the nature of this relationship. Humane and kindly by nature, he detested ostentation and insincerity, and such things could rouse him to anger in debate or private conversation. The concentration and enthusiasm he displayed in his professional work were equally evident in his many other interests—he had long been devoted to ornithology and he was no mean judge of antiques. The 30 years or so of almost daily contact with him has left me with the conviction that, although he would not perhaps have admitted it and certainly made no show of it, he was at heart deeply religious. This, I think, was the fundamental reason for his readiness to give the help and encouragement for which so many of his colleagues and former students (not least myself) will remember him with gratitude and affection.

N. R. HOUSTON, M.D., F.R.C.S.Ed.

Mr. N. R. Houston, formerly consultant surgeon to the Kent County Hospital, Pembury, died suddenly on March 11. He was 67 years of age.

Neil Roy Houston was born in Canada on December 17, 1891, and was educated at the Queen's University, Kingston, Ontario, where he graduated M.D., C.M. in 1922. He came to Great Britain with a travelling fellowship in surgery in 1925, and in the following year obtained the F.R.C.S.Ed. After some postgraduate study in London, and a year as resident surgical officer at Chesterfield, he joined an old-established partnership in general practice in Tonbridge in 1928. His energy and enthusiasm soon won him great popularity, but it was in surgery that his main interest lay. In 1933 he was elected surgeon to the Kent and Sussex Hospital, Tunbridge Wells, an appointment which he held until his retirement three years ago, and a short time afterwards he became consultant surgeon to the Kent County Hospital, as it then was, at Pembury. A member of the British Medical Association for 30 years, he was chairman of the Tunbridge Wells Division in 1945–6.

W. H. P. writes: In the years preceding, and during, the second world war, Houston carried an immense load of work, with his many surgical duties added to the ever-increasing tasks of his practice, but it was not until 1948 that, to the great regret of his many patients, he gave up his general practice and concentrated on surgery. He possessed many of the qualities which make a great surgeon. A very rapid operator, he had an abounding self-confidence which a fine sense of judgment prevented from ever becoming recklessness. His equanimity in the theatre was always complete, and his tolerance and understanding of his assistants, however incompetent or inexperienced they may occasionally have been, made him much loved by all who had the good fortune to work with him. In his earlier, pre-war years he was a general surgeon in the widest sense of the term, and invaded fields which are now regarded as very specialized preserves, but in his later years he concentrated increasingly on abdominal surgery, and much of his work on the colon and rectum was of an outstanding quality. He will be sadly missed by many in a very wide area who will remember him not only as a very able surgeon but as a great character and a true friend. He leaves a widow, a son, and a daughter, to whom our deepest sympathy is extended.

J. C. MACMILLAN, M.B., Ch.B.

Dr. J. C. Macmillan, for many years a well-known general practitioner in Bo'ness, West Lothian, died at Bangour Hospital, West Lothian, on March 7. He was 57 years of age.

John Cairns Macmillan was born on April 5, 1901. Although not a native of Bo'ness, he received his education there, and then studied medicine at St. Andrews University, where he graduated M.B., Ch.B. in 1924. After a spell of hospital work in England, he returned to Bo'ness, where he was in general practice for over 30 years. Always interested in the affairs of the British Medical Association, he was chairman of the Lothians Division in 1948–9 and of the West Lothians Division from 1953 to 1958. He was also a member of the Scottish Council (formerly Committee) from 1954 until his death. He was an enthusiastic Rotarian and an active member of the local curling club. His death came as a great shock to the whole community, where he was much loved and held in high esteem. He leaves a widow, a son, also in the medical profession, and a daughter in the nursing profession.—H. W. H.

HENRY BARDSLEY, M.R.C.S., L.R.C.P.

Dr. Henry Bardsley, honorary consulting dermatologist to the Royal Albert Edward Infirmary, Wigan, and to Southport General Infirmary, died at his home at Birkdale, Lancashire, on February 1. He was 80 years of age.

Henry Bardsley was born at Eccles, Lancashire, on June 23, 1878, and studied medicine at Liverpool University. After qualifying in 1908 he held the appointment of house-surgeon at Liverpool Royal Infirmary. During the first world war he served in the R.A.M.C. as medical officer-in-charge of an officers' V.D. hospital, and as medical officer at the 51st General Hospital with the British Expeditionary Force in France. On demobilization he set up practice in dermatology and venereology in Manchester, Southport, and Wigan. He was appointed to the honorary medical staff of the Royal Albert Edward Infirmary at Wigan in 1922, and honorary consultant dermatologist and venereologist to the newly opened clinics at Southport General Infirmary.

He was also consultant dermatologist to the Southport school health service. A member of the British Medical Association for over 40 years, he was chairman of the Southport Division in 1933–4. On his retirement from the appointments of dermatologist and venereologist at Southport and Wigan infirmaries in 1951, he was appointed honorary consultant dermatologist to both hospitals. He continued in private practice until his death; his keen interest in his work never waned and he was always especially anxious to keep abreast of the times in all dermatological aspects. Many of his patients, both private and hospital, will always be grateful for the comfort he gave them by just listening to their "tales of woe"; he never let them feel that they were wasting his time, because he realized so well what a big part psychology has to play in dermatology, especially when dealing with cases of chronic skin disease. He leaves a widow, a son, and a daughter.—A. R. J.

J. E. BOWES, M.B., C.M.

Dr. J. E. Bowes, who was in general practice at Rishton, Lancashire, for over thirty years, died at a Carlisle hospital on March 2 after a short illness. He was 92 years of age.

Joseph Edward Bowes was born at Langley Mill, Derbyshire, on November 29, 1866, and was educated at local schools and, later, at Borough Polytechnic, London, where he trained as a teacher. After a short time in the teaching profession, he realized that his interests were in medicine, which he began to study at Edinburgh University in 1890. He had a distinguished academic career, gaining a Vans Dunlop prize and the Ettles scholarship, and graduating M.B., C.M., with first-class honours, in 1895. Thereafter he became house-physician at Edinburgh Royal Infirmary and was assistant to the professor of clinical medicine. On completion of his hospital appointments in 1896 he went to Rishton and remained in general practice there for thirty-one years. His practice covered all spheres of medical work: he was, however, particularly experienced in midwifery and attended over 2,700 confinements. In his earlier years in practice his visiting was done on foot and horse-drawn vehicle. Although he became the owner of the first motor-car in the district, he was never an enthusiastic motorist, and very soon reverted to walking on his rounds. A member of the British Medical Association for sixty years, he was chairman of the Blackburn Division in 1923–4. Dr. Bowes spent the first six years of his retirement at Lytham, Lancashire, but after the death of his wife he went with his daughter to live at Borrowdale, Cumberland. He loved his home and garden in their setting of Borrowdale Fells, which were so dear to him. A genial and popular figure, whose pleasant manner earned him the respect and affection of all who came in contact with him, Dr. Bowes retained his keen mind and other faculties to the end. To his younger colleagues his knowledge of current medical affairs and literature was indeed surprising. The death of his son, Mr. Robert Kenneth Bowes, consultant gynaecologist to St. Thomas's Hospital, in 1958, was a sad loss and marked the beginning of his decline in health. He is survived by his daughter.—T. F. K.

C. A. A. LEVER, L.R.C.P.&S.I.

Dr. C. A. A. Lever, who was a well-known general practitioner in Llandudno for more than half a century, died at Llandudno General Hospital on March 6. He was 83 years of age.

Charles Arthur Ashton Lever was born at Birr, Co. Offaly, Ireland, on January 10, 1876, the son of Dr. John Lever, and received his medical education at the Royal College of Surgeons in Ireland and at the Rotunda Hospital, Dublin. After taking the Irish Conjoint diploma in 1898 he held appointments at Mercer's Hospital and at the Northern Dispensary, Liverpool. In 1904, after preliminary assistantships in South Wales and Northwich, he began general practice in Llandudno, where, apart from service in the R.A.M.C. in the first world war, he remained until his death.

A colleague writes: Dr. Charles Lever soon became known at Llandudno for his skill in domiciliary midwifery, and he built up a large practice in which his firm but courteous word became law. He was appointed to the staff of the Llandudno Hospital in 1915, first as a physician and later as radiologist, a post which he held until his retirement in 1949. In the first world war he was in charge of one of the earliest radiological units at Tidworth. In his college days he was a well-known Rugby footballer, and he later developed an interest in golf. A founder member and first captain of the Maesdu golf club, he was also the first president of the North Wales golf club, in which office he remained until his death. He was at one time chairman of the local panel committee and, later, of the local medical committee. Although not socially inclined, he had a host of friends among colleagues and patients, to whom he was affectionately known as "Pop." He will be greatly missed. He leaves one daughter, Mrs. Ingham, a Welsh international golfer.

G. V. BULL, M.B., B.Chir.

Dr. G. V. Bull, who was in general practice at Sandhurst, Kent, for many years, died in hospital on March 2. He was 86 years of age.

George Vernon Bull was the son of William Bull, one-time Senior Master at Harrow School, where he was educated. From Caius College, Cambridge, where he was Sayer scholar, he went on to St. Bartholomew's Hospital, winning the Jeaffreson exhibition. He qualified by taking the London Conjoint diploma in 1899, and two years later obtained the degrees of M.B., B.Chir. After qualification he held the appointments of house-physician at St. Bartholomew's Hospital and house-physician and house-surgeon at the Hospital for Sick Children, Great Ormond Street. Afterwards his life was spent in rural practice at Ashbourne, in Derbyshire; Hoddesdon, in Hertfordshire; and for the last 30 years, partly in retirement, at Sandhurst.

C. G. L. writes: By the death of Dr. G. V. Bull medicine has lost a well-loved country doctor and entomology a life-long lepidopterist. Sometimes his patients would catch glimpses of him performing strange rites with a sheet under sallows on dark nights in March, or by his car, headlights blazing, in the ride of some wood, waiting net in hand, or, tall and statuesque, by some spray of honeysuckle at dusk on a June evening, alert for the blurred appearance of elephant hawk-moths. Strange creatures in match-boxes and cigarette tins would be left at the surgery for identification. He belonged to a long and broad line of naturalist-doctors, men like John Hunter and William Jenner, who got an abiding content from branches of natural history other than medicine. The contagion of their keenness infects others: I can recall at will a near view of the pearly eggs of a poplar hawk-moth on the underside of a leaf which "Verney" Bull gave me as a child of 7 over sixty years ago. He married in 1915 Edith May Newsam, to whom we should like to express our sympathy.

E. A. W. HOUGHTON, M.B., Ch.B., D.M.R.D.

The obituary of Dr. E. A. W. Houghton was printed in the *Journal* of March 14 (p. 723).

J. H. M. writes: The tragic death of Eric Houghton at the age of 32, at the beginning of his career as a specialist—he had just obtained his specialist qualification as a radiologist—has appalled all who knew him. An experienced mountaineer, he was killed at his favourite sport. He was keenly interested in his chosen branch of medicine and already showed promise of being outstandingly good, and there can be no doubt that he would have gone far, both as a practical radiologist and in the sphere of academic work. Those who worked with him respected his

integrity and those who knew him well loved him. He was a good companion and interested in all things. Above all, he was devoted to his home and his family. He will be sadly missed by all of us, and our great sympathy goes out to his young widow and children in their loss.

Medical Notes in Parliament

MENTAL HEALTH BILL

Future of Medical Superintendents

The structure of mental hospital administration, and the future role of the medical superintendent, were canvassed by the standing committee on the Mental Health Bill on March 17. The MINISTER OF HEALTH told the committee that before reaching any decision he wished to give further study to the representations being made by the medical profession.

The discussion arose on Clause 55, which specifies the regulation-making powers of the Minister in connexion with compulsory admission and detention. Dr. EDITH SUMMERSKILL (Warrington, Lab.) moved an amendment adding to the Minister's powers that of defining "the grade and qualification of the responsible medical officers in relation to all or particular classes of hospitals and nursing-homes." With this were taken other proposals to amend Clause 58 (the interpretation clause) requiring that the responsible medical officer should be a medical practitioner "of such grade and qualifications" as the Minister might specify, which Dr. Summerskill suggested; and that he should be a psychiatric consultant, which Sir HUGH LUCAS-TOOTH (Hendon, South, Con.) proposed.

Dr. SUMMERSKILL urged that it was necessary to define the responsible medical officer because, under Common Law, the individual who could be charged with negligence was the person who could be truly said to be in close contact with the patient and have the most responsibility for treatment. It could be said that in a hospital to-day a junior medical officer could be responsible for treatment, although it might be said that the consultant had overall charge. The amendment would give the Minister the opportunity of defining the responsible medical officer in every hospital and nursing-home.

Sir HUGH LUCAS-TOOTH added the argument that the responsible officer should be of sufficient standing. There was a good deal of doubt in the profession about the status of the responsible officer, and fears had been expressed that it might prove—as the Bill was drafted—to be some relatively subordinate person. On the other hand, he had received a letter from a senior member of the profession expressing fears that the drafting might require the medical superintendent to be a responsible medical officer, and that any less person would not comply with the terms. That was going too far in the opposite direction.

Mr. KENNETH ROBINSON (St. Pancras, North, Lab.) turned the debate on to the general question of administration. Under the existing law, he said, the medical superintendent was responsible in law and in fact. What this Bill did was to spread the responsibility; the statutory responsibility for the discharge of a patient was now aligned with the clinical responsibility for a patient's treatment. If that was a reform he welcomed it as a step forward, but it did lead to doubts about the future administrative structure of the mental hospital. Some people in the medical profession considered that the medical superintendent, as now understood, would be abolished. Others, including many superintendents, believed their position would be maintained, apart from the one function of right of discharge being spread to the "responsible medical officer." In the past the omnipotence of the medical superintendent was probably an essential feature, but it gave rise to what was called the hierarchical structure that had deterred many good men from entering the mental hospital service. On the other hand, there was a need for some direction of overall medical policy in a mental hospital.

He suggested a modification of the present system in which the medical superintendent would be appointed for a period of three, four, or five years. The appointment would be renewable, but it would not be automatically renewed. If during the period the superintendent lost the confidence of his medical colleagues or of the management committee, quite smoothly, without any slur on his clinical reputation, they would be enabled to make a change.

In Clinical Charge

Mr. D. WALKER-SMITH first declared that the definition of the responsible medical officer—"the medical practitioner in charge of the treatment of the patient"—meant the doctor who was in clinical charge and not answerable to any other doctor: the doctor who could put up the notice said to have been put up by President Truman in his office, "The buck stops here." The test was not day-to-day attention, but ultimate supervision. It was the consultant who had the ultimate responsibility of supervision, and not the junior doctor who gave the day-to-day treatment.

The proposed consultant definition would not do, because the responsible medical officer would not in all cases be a consultant. The doctor satisfying the test of supervision might sometimes be a senior hospital medical officer who had independent clinical charge of some patients. There might also be special circumstances in which other members of the medical staff were in charge, either temporarily or otherwise.

Profound changes in the law were being made which obviously affected the functions of the medical superintendent. The managers were now to be the detention authority, and the responsible medical officer in clinical charge would have the functions relating to discharge, renewal, and leave of absence. The existing regulations obviously became impossible, being linked to terminology which would become obsolete when the Bill was passed. The position of the medical superintendent must be considered in relation to the new service. As he saw it, in addition to the transfers of functions already mentioned, the position would alter in time for other reasons: there would be more in-patient treatment in general hospitals and in special wards, and progressively more out-patient treatment. All this would, in the long run, tend to replace the large mental hospital, and reduce the need for a medical superintendent in the accustomed sense. There was also a tendency for the setting up of medical staff committees in mental hospitals. That meant medical policy determined more by the collective view than by what had been called the hierarchical principle. But there was a greater need for single leadership in mental hospitals because of the organization in the hospitals of a therapeutic community, a need for a father figure.

He had received representations from the Royal Medico-Psychological Society asking for new regulations defining the position of the medical superintendent as chief officer in the new context. He was expecting to receive other professional representations, not necessarily pointing in the same direction. He was considering all these matters, but had not yet come to any definite conclusion.

After further discussion, the amendments were withdrawn and the clause agreed to.

QUESTIONS IN THE COMMONS

Psychiatric Social Workers

Mr. S. SWINGLER (Newcastle-under-Lyme, Lab.), who questioned the Minister of Health on March 16 about the number of psychiatric social workers employed in Staffordshire in comparison with some other counties, expressed the view that there was a terrible inadequacy in this service. Many of the workers felt that there was complete lack of co-ordination between those employed in hospitals and those employed by local authorities and the Ministry. Mr. R. THOMPSON, the Parliamentary Secretary, agreed that there was a great need for more psychiatric social workers, but pointed out that much mental welfare work could be done by less highly qualified people. The

report of the Younghusband Committee, which was expected at any time now, would throw some light on this aspect of the service.

Mr. K. ROBINSON (St. Pancras North, Lab.) said it would be impossible to develop proper community mental health services unless more psychiatric social workers were recruited and trained. What was the Ministry doing to look after that? Mr. THOMPSON told him that there was a special scheme of training allowances for students to assist recruitment, and he expected it to have beneficial results.

Vaccination and Smallpox

The MINISTER OF HEALTH informed Mr. S. VIANT (Willesden, West, Lab.) on March 17 that the provisional total of deaths in 1958 from vaccination, vaccinia, post-vaccinal encephalitis, or any other results of vaccination was seven. Five were under the age of 1 year, one was aged 2, and one aged 68. One death from smallpox was registered in 1958, that of a man aged 54.

Alcohol and the Motorist

Mr. SOMERVILLE HASTINGS (Barking, Lab.) asked the Minister of Transport on March 18 what legislative action, by way of the amendment of the Traffic Act, 1956, or otherwise, was contemplated to implement the finding of the Drew report* that chemical tests were both reliable and administratively feasible. Mr. H. WATKINSON replied that he was most grateful to Professor Drew for the valuable addition to their knowledge which his report had given. It did not, however, in his view, in itself provide a basis on which legislative proposals could be framed for presentation to Parliament. He proposed to have further discussions on the general issue with the Medical Research Council.

*Drew, G. C., Colquhoun, W. P., and Hazel, A. L., *Brit. med. J.*, 1958, 2, 993.

Medico-Legal

SNAILS AND STATUTORY DUTIES

[FROM OUR LEGAL CORRESPONDENT]

At the Westminster County Court on March 2 a lady who stated that she became ill after eating snails was held to have no cause of action for damages under the Food and Drugs Act, 1955, against the vendor (*The Times*, March 3). Under Section 8 of that Act it is an offence to sell food which is unfit for human consumption. Section 106 states the maximum penalties for offences under the Act to be a fine of not more than £100 or imprisonment for not more than three months or both. The judge decided, however, that this Statute imposes criminal penalties only, and did not support a civil action for damages to compensate the buyer for her injuries.

Where a Statute imposes a duty on certain persons, or on persons generally, it is a question of construction of the individual Statute whether that duty is enforceable by criminal proceedings only, or by a civil action for damages only, or by both. Under some Statutes private persons are vested with rights regarding the duty imposed: under others the rights are vested in the State only.

When the Individual Can Sue

In general, if a Statute imposes a duty but prescribes no sanction in the form of punishment or compensatory damages, then either an action for damages or an indictment for a misdemeanour can be brought. But where a Statute imposes a duty and enforces its performance in a specified manner, the general rule is that performance cannot be enforced in any other way. Whether the general rule is to prevail or an exception to the general rule is to be admitted depends on the scope and language of the Statute and on considerations of policy and convenience. If the words of the Statute show that its scope and purpose is to protect particular persons as opposed to the public at large, the courts will allow such persons a civil action in addition to the statutorily prescribed remedy. Such intention is rarely stated explicitly, however, and must be inferred from the Statute as a whole. For example, the courts have held that the Factories Acts are, in general, intended for the protection of workers in factories and workshops. But Section 11 of the Betting and Lotteries Act, 1934, on the other hand, has been held to be intended merely to regulate the conduct of racecourses, although some bookmakers might incidentally benefit from the enforcement of that Section. Both factory-owners and racecourse-owners are respectively made liable to criminal penalties. But while the factory worker can sue for damages under the first Statutes, the bookmaker cannot do so under the latter.

Statutes which impose duties on vendors have generally been held to be for the protection of the public as a whole, not for the protection of individual purchasers. Hence the lady who ate snails had no action under the Food and Drugs Act in respect of the injuries she suffered.

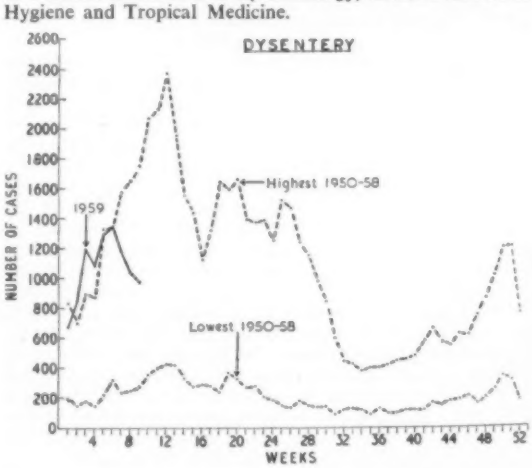
Other Remedies

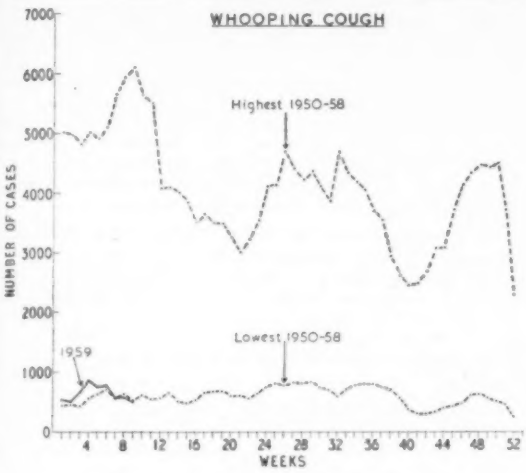
This, of course, would not extinguish any independent rights she might have had at Common Law, for instance an action in negligence or an action on a breach of an express or implied warranty or condition on the sale. If, for instance, the vendor ought to have foreseen that the snails would make the lady ill when she ate them, he would be liable to pay damages for negligence. If he had expressly warranted them to be in good condition, he would be liable in damages upon that warranty. He would also be liable upon an implied condition, if it was in the course of his business to supply snails and either the lady showed that she relied on his judgment that the snails were fit to eat or she bought them by description (i.e., not by pointing to a specific lot of snails on the slab). Presumably, in this case the lady could not prove any of these additional matters. To succeed in contract it would have had to be with her that the contract was made.

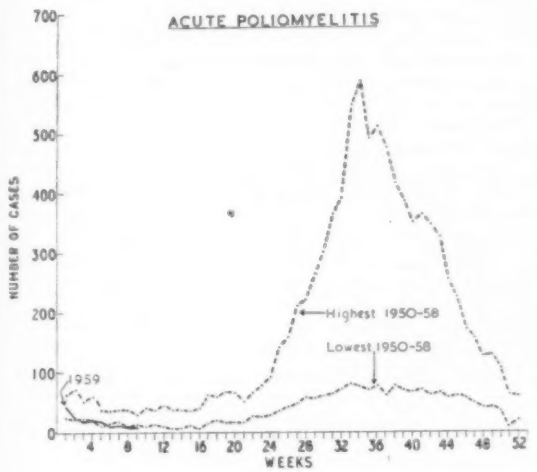
Vital Statistics

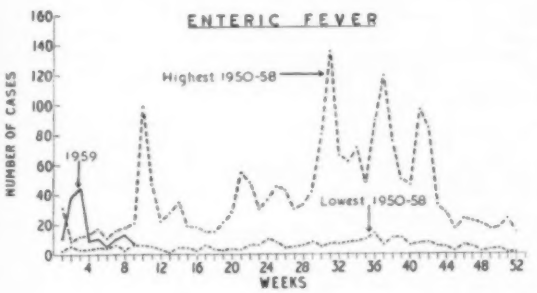
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Smallpox at Liverpool

A second case of smallpox had been reported in Liverpool at the time of going to press on March 21. We are indebted to Professor A. B. SEMPLE for the following information. The patient is a hospital technician, aged 35, and had been in contact on March 7 with the fourth-year medical student found subsequently to have smallpox (*Journal*, March 14, p. 731). A characteristic prodromal rash appeared on the technician on March 18. He had been vaccinated in the past two years, and several times previously. The source from which the medical student was infected had not been traced at the time of going to press.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 7** (No. 9) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	3	1	1	0	1	3	0	1	0	1
Dysentery ..	973	82	146	11	2	1,333	159	226	16	1
Encephalitis, acute	1	0		0		3	2		0	
Enteric fever:										
Typhoid ..	1	0	0	0		2	0	0	0	
Paratyphoid ..	6	1	0	0		4	1	2(B)	0	39 (B)
Food-poisoning ..	112	18	3	1		124	20	16	0	
Infective enteritis or diarrhoea under 2 years				10	22				15	16
Measles*	23,512	1360	897	677	888	4,383	110	94	35	47
Meningococcal infection	37	3	19	1	3	25	5	11	0	1
Ophthalmia neonatorum	21	4	3	0		40	5	4	0	
Pneumonia† ..	2,583	162	674	23	38	773	59	348	11	6
Poliomyelitis, acute:										
Paralytic ..	9	2	1	0		10	0	0	0	4
Non-paralytic ..	0	0	0			5	2			
Puerperal fever§ ..	284	35	10	0		226	39	17	1	
Scarlet fever ..	1,207	50	65	37	11	797	59	75	20	17
Tuberculosis:										
Respiratory ..	444	56	66	4		573	90	94	18	
Non-respiratory	61	2	17	3		64	5	6	1	
Whooping-cough	500	28	42	59	85	524	26	36	5	11

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	1	0	0	0	0	0
Dysentery ..	1	1		0		1	0		0	
Encephalitis, acute		0			0		0			
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	8	0	2	0	1	4	0	0	0	0
Influenza	1,399	103	28	5	7	111	2	1	0	1
Measles		1	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	1		
Pneumonia ..	1,809	146	82	26	19	738	51	36	14	7
Poliomyelitis, acute	2	1		0	0	1	0		0	0
Scarlet fever ..		0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory ..	147	12	9	0	2	112	3	13	0	6
Non-respiratory		0	0	0	0		0	0	0	0
Whooping-cough	0	0	0	2	1	0	0	0	0	0
Deaths 0–1 year ..	369	32	34	12	11	355	21	33	14	6
Deaths (excluding stillbirths) ..	15,551	1407	860	164	238	11,389	826	739	142	157
LIVE BIRTHS ..	15,642	1424	1082	276	378	13,844	1164	979	215	421
STILLBIRTHS ..	327	24	25			330	22	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New Cardiff Medical Centre.—Details of an architectural competition for the new medical teaching centre at Cardiff will be announced early in April by the board of governors of the United Cardiff Hospitals, and the council of the Welsh National School of Medicine (see *Journal*, October 4, 1958, p. 866). Among the assessors who will adjudicate on the designs received are Dr. A. TREVOR JONES, provost of the Welsh National School of Medicine, and Dr. A. R. CULLEY, medical member of the Welsh Board of Health. The centre will be built on a 50-acre site at the Heath, Cardiff, and will include a teaching hospital of 650 beds, with a possible future extension to 800 beds, a medical school, a dental hospital, and a dental school, together with the usual residential accommodation.

P.H.L.S.: Diagnosis of Toxoplasmosis.—Routine examination of antibodies to toxoplasma, which has hitherto been carried out by Professor C. P. Beattie at Sheffield and Dr. I. A. B. Cathie or Dr. J. C. W. Macfarlane at the Hospital for Sick Children, Great Ormond Street, London, will from April 1, 1959, be transferred to the public health laboratories at Leeds and Sheffield. Specimens from Hospital Regions 1, 2, 3, 4, 13, and 14, and from Scotland—i.e., North Britain down to and including the counties of Cheshire, Derby, Leicester, Huntingdon, Cambridge, and Suffolk—should be sent to Dr. G. B. LUDLAM, at the Public Health Laboratory, Bridle Path, York Road, Leeds, 15 (Tel.: Leeds 64-5011); and specimens from Hospital Regions 5 to 12 to Dr. D. G. FLECK, Public Health Laboratory, Cockett Road, Swansea (Tel.: Swansea 24041/2).

Carlsberg-Wellcome Travelling Research Fellowship.—Applications are invited for the Carlsberg-Wellcome travelling research fellowship, 1959–60, for a British research worker. The closing date for applications is April 30.

The object of these fellowships is to encourage co-operation, on an exchange basis, between Danish and British research workers in any branch of the natural sciences which has a bearing upon human and animal medicine. One fellowship annually is awarded to a candidate from the United Kingdom for a year's work in Denmark and one annually to a Danish candidate for a year's work in the United Kingdom. The stipend may range from £800 to £1,200 per annum (or the equivalent sums in Danish kroner), travelling and some incidental expenses being provided in addition. The tenure of the awards will start in September, 1959.

Inquiries from candidates in the United Kingdom should be addressed to the Assistant Scientific Secretary, The Wellcome Trust, 52, Queen Anne Street, London, W.1.

Empire Rheumatism Council.—The council has awarded a research fellowship to Dr. D. M. WEIR, of the Canadian Red Cross Memorial Hospital, Taplow, who is studying the anti-nuclear serum factor or factors in disseminated lupus erythematosus and other connective tissue diseases. Two Geigy travelling fellowships have been awarded: one to Dr. H. WYKEHAM BALME, of St. Bartholomew's Hospital, who will study under Professor Walter Bauer at Boston, U.S.A., and the other to Dr. MADELINE KEECH, of the General Infirmary, Leeds, who will spend four months at the University of Rochester, U.S.A., studying the newer techniques in research into rheumatic disorders.

Chiropody for Old People.—The National Corporation for the Care of Old People believes that there is an urgent need for chiropody, at least for old people, to be brought into the National Health Service, and points out that the chiropody service recently announced by the Minister of Health, Mr. WALKER-SMITH, makes no provision, at present, for treating old people, many of whom are house-bound, in their own homes. These views, and possible solutions to the problems they raise, are discussed in a booklet published by the Corporation on March 18 (*A Chiropody Service for Old People: A Study of Present Needs*, price 1s.).

75th Anniversary.—The Medical Sickness Annuity and Life Assurance Society was founded in 1884. It was founded by doctors for doctors, and was run by doctors, said Lord EVANS when proposing the Society's health at a commemorative dinner last week. But he noted the presence of a layman to whom this doctors' society owes so much—Mr. BERTRAM SUTTON, who entered the society's service in 1899 and retired 14 years ago, to be succeeded by Mr. HEATH. Lord EVANS paid a handsome tribute to the Society's President, Mr. R. J. MCNEILL LOVE.

Sir Gordon Gordon-Taylor 81.—News spread round the tables at the 11th anniversary dinner of the Faculty of Anaesthetists on March 18 that it was Sir GORDON GORDON-TAYLOR'S eighty-first birthday, and when he proposed the Faculty's toast he was greeted with an affectionate ovation. Dr. GEOFFREY ORGANE, Dean of the Faculty, presided over a large gathering in the Hall of the Royal College of Surgeons.

Dr. J. E. Salk, Commonwealth professor of experimental medicine, University of Pittsburgh, is to receive the degree of Doctor of Science *honoris causa* of the University of Leeds when he visits this country for the health congress of the Royal Society for the Promotion of Health, to be held at Harrogate from April 27 to May 1. It is expected that the degree congregation will be held on May 2.

University of Birmingham.—The title of University Research Fellow in the department of medicine has been given to Dr. E. V. COX, senior medical registrar, United Birmingham Hospitals, during the tenure of his present appointment.

University of Edinburgh.—At a meeting of the Court on March 16 Dr. GUY BOISSARD was appointed lecturer in bacteriology with effect from May 1, and Dr. W. H. SCHUTT temporary lecturer in child life and health from October 1.

University of Leeds.—The Council of the University has agreed that the following be promoted to the title and status of senior lecturer from October 1: Dr. W. K. J. WALLS, lecturer in anatomy, Dr. J. M. ROBERTS, lecturer in psychiatry, and Mr. F. G. SMIDDY, lecturer in surgery.

University of St. Andrews.—On June 30 the degree of Doctor of Laws at the University will be conferred on Sir GEORGE LINDOR BROWN, F.R.S., Jodrell professor of physiology, University College, London, and emeritus professor of anatomy at the University of St. Andrews.

Dr. K. G. Bergin, at present chief medical officer of British Overseas Airways Corporation, has been appointed director of both personnel and medical services, which have now been combined. He has held a current pilot's licence for 25 years and has made a special study of aviation medicine.

Dr. G. B. Dowling, consulting dermatological physician to St. Thomas's Hospital, received the honorary degree of M.D. at the Afrikaans University of Pretoria on March 21. Dr. Dowling is on a lecture tour in the Union of South Africa.

"Common Ailments in Babies."—This *Family Doctor* booklet by Professor R. S. ILLINGWORTH, professor of child health at the University of Sheffield, is now on sale (price 1s.). The framework of the booklet is supplied by Professor Illingworth's articles in the *Family Doctor*, but they have been extensively revised and new material added.

COMING EVENTS

"On Call to a Nation."—This documentary film will be repeated on B.B.C. Television on Sunday, April 5, at 9.30 p.m.

Faculty of Radiologists.—A provincial meeting will be held in Glasgow in the Lecture Room, Department of Pathology, Western Infirmary, on April 11. Details from the Secretary of the Faculty, 47, Lincoln's Inn Fields, London, W.C.2. Applications for accommodation by April 3.

British Occupational Hygiene Society.—The tenth conference, on "The Control of Dust and Fume in Industry," will be held on April 14 and 15 at Stephenson Hall (University of Sheffield), Oakholme Road, Sheffield, 10. Details from Dr. D. TURNER, the Associated Ethyl Company, Ltd., Ellesmere Port, Cheshire.

15th International Tuberculosis Conference.—Istanbul, September 11–18. Further details from the secretariat of the International Union against Tuberculosis, 15, rue Pomereu, Paris, 16.

European Congress of Cardiology.—The third congress will be held in Rome from September 18 to 25, 1960. Details from the Secretariat, E.C.C., Clinica-Policlinico, University of Rome, Italy.

International Embryological Conference.—Sponsored by the *Journal of Embryology and Experimental Morphology*, September 21–24, at the Collège de France, Paris. Details (after June 1) from Dr. L. BRENT, Department of Zoology, University College, Gower Street, London, W.C.1.

Ross Institute of Tropical Hygiene.—The annual course for laymen will be held from July 6 to 10. Subjects covered include malaria and its control, and other tropical diseases. Details from L. G. PONSFORD, Ross Institute of Tropical Hygiene, London School of Hygiene and Tropical Medicine, Keppel Street (Gower Street), London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Tuesday, March 31

ROYAL ARMY MEDICAL COLLEGE.—5 p.m., Brigadier R. R. Bomford: Essentials of Diabetic Management.

ROYAL STATISTICAL SOCIETY: MEDICAL SECTION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Mr. W. Z. Billewicz: Maternal Height and Child-bearing Performance.

Wednesday, April 1

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Dr. I. Friedmann, Dr. D. A. Osoorn, and Dr. A. L. Jeanes: clinical pathological conference.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Dr. I. Gordon: "Old People's Flats."

Thursday, April 2

ALFRED ADLER MEDICAL SOCIETY.—At Royal Society of Medicine, 8.15 p.m., Dr. E. K. Ledermann: Existential Psychotherapy.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Selby's, 26, Hanover Street, W., 6.30 p.m., annual dinner dance.

ROYAL EYE HOSPITAL.—5.30 p.m., Dr. T. H. Whittington: Aspects of Refraction Work—(1) Recognition of Abnormal Vision.

Friday, April 3

BIOCHEMICAL SOCIETY.—At Department of Biochemistry, University College, Gower Street, W.C., 10.30 a.m., annual general meeting.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Dr. I. Friedmann: Recent Advances in Chemotherapy.

ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., William Mackenzie Lecture by Professor I. C. Michaelson: Error and Discovery in Fundal Disease.

●SHEFFIELD UNIVERSITY AND SHEFFIELD MEDICO-CHIRURGICAL SOCIETY.—At Firth Hall of University, Western Bank, 8.15 p.m., 2nd Arthur Hall Memorial Lecture by the Rt. Hon. Lord Kilmuir: Medicine and the Law.

Saturday, April 4

MIDLAND THORACIC SOCIETY.—3 p.m., visit to West Heath Hospital, Birmingham, for clinical meeting and annual general meeting.

Sunday, April 5

UNIVERSITY COLLEGE HOSPITAL.—10.15 a.m., meet in Front Hall of main Hospital. Lecture-demonstration for general practitioners. Clinical demonstration by Mr. D. P. Greaves and Mr. C. Dee Shapland: Eye Conditions Commonly met in General Practice, followed by film on modern ophthalmic treatment.

APPOINTMENTS

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—R. J. Stout, M.B., B.S., F.F.A. R.C.S., Consultant Anaesthetist, North Cambridgeshire Hospital Group; Y. P. Kapur, M.B., B.S., D.L.O., Ear, Nose, and Throat Registrar, Norfolk and Norwich Hospital and Jenny Lind Children's Hospital; P. B. Gupta, M.Ch.Orth., F.R.C.S.Ed., Orthopaedic Registrar, Norfolk and Norwich Hospitals; P. C. Uthappa, M.B., B.S., Surgical Registrar, North Cambridgeshire Hospital, Wisbech; V. N. Shrikhande, M.B., B.S., Surgical Registrar, County Hospital, Doddington; R. Gaind, M.B., B.S., F.R.F.P.S., Medical Registrar, West Norfolk and King's Lynn General Hospital; J. L. Hunter, M.B., Ch.B., Anaesthetic Registrar, West Norfolk and King's Lynn General Hospital; K. H. Nickol, M.B., B.S., M.R.C.P., Senior Registrar in Chest Medicine, Cambridge Area Chest Clinic; Anne Ambrose, M.B., B.S., Registrar in Psychiatry, Hellesdon Hospital; Ilse Pollock, M.D., Paediatric Registrar, Jenny Lind Children's Hospital, Norwich; S. K. Ghosh, M.B., B.S., Orthopaedic Registrar, King's Lynn Hospital Group; H. Hardy, M.B., Ch.B., D.O., Consultant Ophthalmic Surgeon, Ipswich and East Suffolk Hospital Group; M. J. Clarke-Williams, M.B., B.Chir., Assistant Physician in Geriatrics, Ipswich and East Suffolk Hospital Group.

KIRBY, CHRISTINE, M.B., B.S., D.P.H., D.C.H., D.Obst.R.C.O.G., Assistant Medical Officer to Principal Medical Officer, Imperial Chemical Industries Ltd., Head Office, Millbank, London, S.W.1.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—G. W. Csonka, M.D., M.R.C.P., M.R.C.P.Ed., Consultant Venereologist, Central Middlesex Hospital; L. A. Hersov, M.D., D.P.M., Consultant Psychiatrist, Child Guidance Training Centre; J. R. Raeside, M.B., Ch.B., M.F.Hom., Senior Hospital Medical Officer, Royal London Homoeopathic Hospital; D. H. Malan, B.M., B.Ch., D.P.M., Assistant Psychiatrist (S.H.M.O.), Tavistock Clinic; W. Brumfitt, M.D., M.R.C.P., Consultant Clinical Pathologist, Edgware General Hospital; I. W. Winchester, M.Ch.Orth., F.R.C.S.Ed., Consultant Traumatic and Orthopaedic Surgeon, Whittington Hospital; B. Schwartz, M.D., D.P.H., Consultant Dermatologist, Barnet General Hospital; J. M. Davis, M.Chir., F.R.C.S., Consultant General Surgeon, Whittington Hospital; P. G. Woolf, M.R.C.S., L.R.C.P., D.P.M., Assistant Child Psychiatrist (S.H.M.O.), Hertfordshire Child Guidance Service.

SOUTH-EASTERN REGIONAL HOSPITAL BOARD (SCOTLAND).—I. E. W. Gilmour, M.B., Ch.B., F.R.C.S.Ed., Consultant Surgeon, Deaconess Hospital, Edinburgh; W. McNaught, M.D., Consultant Clinical Pathologist, Scottish Borders Group of Hospitals.

UNITED MANCHESTER HOSPITALS.—A. R. Anscombe, M.S., F.R.C.S., Part-time Consultant Surgeon; T. B. Fitzgerald, M.B., Ch.B., F.R.C.S.Ed., M.R.C.O.G., Part-time Consultant Obstetrician and Gynaecologist; H. B. Torrance, M.B., Ch.B., F.R.C.S.Ed., Part-time Consultant Surgeon.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bagchi.—On March 5, 1959, at Manor Hospital, Walsall, Staffs, to Eileen, wife of Dr. J. C. Bagchi, of Bentley, Darlaston, Staffs, a brother for Anita and Amanda.

McConnachie.—On March 8, 1959, in London, to Margaret (formerly Langan), and Dr. R. W. McConnachie, a son.

Morley.—On February 18, 1959, to Emily (formerly Mochrie), M.B., B.S., wife of John W. Morley, M.B., Ch.B., of McCain, North Carolina, U.S.A., a son—John William.

DEATHS

Attwater.—On March 7, 1959, in Middlesex, Geoffrey Lewis Attwater, M.D.

Bachtin.—On March 15, 1959, in a nursing-home, Maidenhead, Berks, Constance Mary Alix Bachtin, M.B., Ch.B., late of Birmingham.

Bamfield.—On March 8, 1959, at his home, Purser's Piece, Peaslake, Surrey, Harold John Kinahan Bamfield, C.B., D.S.O., M.R.C.S., L.R.C.P., Major-General, I.M.S. (retired), aged 88.

Budden.—On March 9, 1959, at White Lodge, Bildeston, Suffolk, Jean Effie Budden, M.D., aged 85.

Bursey.—On March 5, 1959, Elspet Bursey, M.B., Ch.B., of Lewannick, Cornwall, aged 68.

Drake.—On March 14, 1959, on board ship, Japan, James Drake, L.R.C.P.&S.Ed., L.R.F.P.S., aged 56.

Edwards.—On March 13, 1959, at Hollowcombe, Lustleigh, Devon, Cyril Kent Dodwell Edwards, T.D., M.B., Ch.B., late of Ainsdale, Southport, Lancs.

Galbraith.—On March 8, 1959, at Launceston Hospital, Cornwall, Douglas Hugh Aird Galbraith, *M.C.*, M.R.C.S., L.R.C.P.

Gibson.—On March 6, 1959, at St. Bartholomew's Hospital, London, E.C., William Robert Gibson, F.R.C.S., D.P.H., D.T.M.&H., formerly of Madras, India, Ealing, London, W., and Hove, Sussex, aged 87.

Houston.—On March 11, 1959, Neil Roy Houston, M.D., F.R.C.S.Ed., of Hargate House, Tunbridge Wells, Kent.

Irvine-Fortescue.—On March 10, 1959, at Aberdeen, Archer Irvine-Fortescue, D.S.O., M.B., Ch.B., D.L., J.P., Colonel, A.M.S. (retired), of Kingcausie, Kincardineshire, and Swanbister, Orkney, aged 78.

Kennedy.—On March 19, 1959, at Bulawayo, Southern Rhodesia, Alan Francis Kennedy, O.B.E., M.D., F.R.C.P.I.

Kitching.—On March 16, 1959, at 4, Ashfield, Wetherby, Yorks, Robert Lacy Kitching, M.B., B.S., aged 69.

Marcuse.—On March 17, 1959, at 114, Hurlingham Road, London, S.W., Herman Marcuse, M.D.

Martin.—On March 10, 1959, Thomas Joseph Martin, M.B., Ch.B., of 161, Ashton New Road, Beswick, Manchester, aged 51.

Maxton.—On March 15, 1959, at Auldgirth, Dumfries, James Maxton, M.B., Ch.B., D.P.H., D.I.H., of Beechwood, Barrhead, Renfrewshire.

Murray.—On March 12, 1959, at Sevenoaks, Kent, John Hanna Murray, C.I.E., M.D., D.P.H., D.T.M.&H., Lieutenant-Colonel, I.M.S., retired, of Mandeys, Brasted, Kent, aged 85.

Murray.—On March 12, 1959, at Calvine, Lundin Links, Fife, Peter Murray, M.B., F.R.C.S.Ed., aged 84.

Poole.—On March 17, 1959, at Bryncoed, Rhayader, Radnorshire, John Douglas O'Mahony Poole, M.B., Ch.B.

Porter.—On March 18, 1959, in hospital, James Houston Porter, M.R.C.S., L.R.C.P., of London, W.

Rink.—On March 6, 1959, at Edenbridge Hospital, Kent, Ernest Herrmann Rink, B.M., B.Ch., F.F.A. R.C.S., aged 54.

Ritchie.—On March 19, 1959, at 207, Sandgate Road, Folkestone, Kent, Thomas Clark Ritchie, O.B.E., M.D., aged 72.

Saint.—On March 11, 1959, in hospital, Arthur Paul Saint, *M.C.*, M.B., B.Ch., of Lavender Cottage, Manor Road, Angmering-on-Sea, Sussex, formerly of Leamington Spa, Warwicks, aged 69.

Stuart.—On March 15, 1959, at Tythe Barn, Kirkbymoorside, Yorks, John Latimer Stuart, M.B., B.Ch., D.T.M.&H., D.P.H.

Webster.—On February 28, 1959, at The Yews, Longford, Coventry, Warwicks, Harold George Webster, M.R.C.S., L.R.C.P., aged 83.

West.—On March 10, 1959, at his home, Lower Woodmanton, Woodbury, Exeter, Devon, Basil Massey Rowe West, M.R.C.S., L.R.C.P.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Detecting Cancer Cells in Blood Stream

Q.—*Is there a technique for finding malignant cells in the peripheral blood of a patient with cancer, and does the malignant cell count rise during operation and drop afterwards? Is the technique a practicable one for the average small hospital laboratory?*

A.—Systematic attempts to isolate or identify malignant cells in the blood stream were carried out by Pool and Dunlop in 1934.[1] Engell[2] reported the identification of tumour cells in the blood stream during operation as well as in those patients with advanced malignant disease. Blood specimens taken at operations from veins draining the tumour frequently contained tumour cells. Fisher and Turnbull[3] demonstrated tumour cells in the mesenteric venous blood in patients with cancer of the colon or rectum.

The subject was discussed by Sandberg and Moore,[4] who described the method which was found to give the best results. It appears that the technique could be carried out by a competent pathologist in a small hospital laboratory where the necessary apparatus is available. Considerable knowledge is necessary of the morphology of the normal cellular elements present in the blood as well as of other cells which may be confused with cancer cells. The preliminary observations of these workers paralleled those of Engell, who found an equal number of tumour cells in the regional veins both before and after manipulation of the tumour in the abdominal cavity. They pointed out, however, that this may not be true for a malignant pulmonary tumour.

An annotation on this subject was published in last week's *Journal* at page 774.

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1 Pool, E. H., and Dunlop, G. R., *Amer. J. Cancer*, 1934, **21**, 99.
2 Engell, H. C., *Acta chir. scand.*, 1955, suppl. 201.
3 Fisher, E. R., and Turnbull, R. B., *Surg. Gynec. Obstet.*, 1955, **100**, 102.
4 Sandberg, A. A., and Moore, G. E., *J. nat. Cancer Inst.*, 1957, **19**, 1.

Relief of Pain in Osteitis Deformans

Q.—*What relief can be given, beyond the usual analgesics, for pain in a case of osteitis deformans?*

A.—The relief of pain in osteitis deformans is difficult and frequently impossible. Apart from analgesics, which are the real method of control, there are two rather unsatisfactory surgical procedures. It has been said that linear osteotomy will relieve pain. This is an operation that has been done for many years, but from the general lack of enthusiasm for it it is difficult to believe that anyone has had reasonable success. The more recent alternative has been periarterial sympathectomy of the nutrient vessel of the bone affected, in the belief that this would divide pain-carrying fibres. Results are doubtful, and it is probable that a good deal of the pain comes from the periosteum. When constant severe pain arises sarcoma must always be thought of, since there is a fairly high percentage of patients in which metaplasia takes place.

B.C.G. Revaccination

Q.—*If, after B.C.G. vaccination, the tuberculin skin test either fails to convert to positive or gradually reverts to negative, is revaccination imperative? Has congenital gamma-globulin lack any significance in B.C.G. work?*

A.—As there is as yet no test for acquired resistance after B.C.G. vaccination, conversion from tuberculin-negative to tuberculin-positive is accepted for practical purposes as the criterion of successful vaccination. Failure to convert is thus taken in practice to mean an unsuccessful vaccination, and reversion from tuberculin-positive to tuberculin-negative to indicate loss of acquired resistance; revaccination should be carried out in each case. Wells[1] has shown in guinea-pigs that acquired resistance after B.C.G. vaccination does not outlast allergy by more than six months.

No study has yet been made of the effect of congenital hypogammaglobulinaemia on B.C.G. vaccination. Parkes,[2] in his study of hypogammaglobulinaemia and tuberculosis, collected reports of isolated cases that had been injected with B.C.G.; in no instance did any ill effect result.

REFERENCES

1 Wells, A. Q., and Wylie, J. A. H., *Brit. J. exp. Path.*, 1952, **33**, 405.
2 Parkes, R., *Brit. med. J.*, 1958, **1**, 973.

"H3"

Q.—*Can you give me any information about H3, which is said to be a derivative of procaine and to have been used in geriatric cases?*

A.—"H3" is not a derivative of procaine but simply a 2% solution of procaine made up at *p*H 4.2–5. The treatment which has been claimed in Bucharest to cause rejuvenation and spectacular cures of arthritis, arteriosclerosis, and other diseases of old age has been the intramuscular injection of 5 ml. of this solution every other day for 12 weeks. The intravenous injection of procaine as a systemic analgesic was at one time used with enthusiasm in the treatment of rheumatic diseases, but was abandoned after it was shown[1] to have very little more analgesic effect than a placebo administered by the same technique, and also because of the high incidence of toxicity. In reports on H3 which are available in this country[2 3] it is said that no toxic effects have been seen in some 6,000 cases; no mention is made of any control groups given placebo treatment. It would be remarkable if these powerful therapeutic effects attributed to procaine had not been observed elsewhere in a drug so widely used. It is known to have a quinidine-like effect, but this is too transient to be of any value. It is hydrolysed in the body to give *p*-aminobenzoic acid and diethylaminoethanol, and it has been suggested[4] that the mental stimulation and euphoria reported to occur after procaine are due to the latter substance, which has recently been introduced as a "psychic energizer."[5] But the evidence for the effectiveness of this substance is itself scanty.

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1 Keats, A. S., d'Alessandro, G. L., and Beecher, H. K., *J. Amer. med. Ass.*, 1951, **147**, 1761.
2 Aslan, A., *Ther. Umschau*, 1956, **13**, 165.
3 Parhon, C. I., and Aslan, A., *Rev. Sci. méd. (Bucuresti)*, 1957, No. 2, 5.
4 Lüth, P., *Dtsch. med. J.*, 1958, **9**, 435.
5 *Brit. med. J.*, 1959, **1**, 298.

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